UNIVERSITEIT GENT

FACULTY OF SCIENCES

THESIS SUBMITTED TO OBTAIN THE DEGREE OF DOCTOR OF SCIENCE: CHEMISTRY

SOLID PHASE SYNTHESIS OF STRUCTURALLY DIVERSE 1,2,5-BENZOTHIADIAZEPIN-4-ONE-1,1-DIOXIDES, 1,2,5-THIADIAZEPIN-4-ONE-1,1-DIOXIDES AND 1,2,6-BENZOTHIADIAZOCIN-5-ONE-1,1-DIOXIDES

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Dankwoord

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CHAPTER I: INTRODUCTION

1. MEDICINAL CHEMISTRY, FROM FOLK MEDICINE TO COMPUTER ASSISTED DRUG DESIGN

Although the birth of medicinal chemistry can be set at the start of the 20th century, its real origin lies in a far more distant past. Mankind has been confronted with disease since its very existence and has tried to deal with it in several ways. And although the general belief was that disease had a supernatural origin and therefore the cure should be sought in prayer and religious rituals, he quickly noticed that Nature was a useful tool in this fight. He learned to use plant, animal or mineral-based medicines and orally passed this knowledge on to future generations, giving rise to traditional medicine. The first written records of this traditional medicine are about 5000 years old and were found in Mesopotamia, currently Iraq, describing the medicinal use of certain plants. These were followed by Egyptian, Indian and Chinese writings, which contained cures and treatments based on plant, animal and mineral extracts but also detailed observations and descriptions of different diseases. In Europe, a lot of this medicinal knowledge was introduced by the Greeks and further developed by the Romans. One of the most important historical works written during that period was *De Materia Medica* by Dioscorides, containing an extensive review of more than 1000 nature-based drugs. It was copied, translated and used as a reference in Europe and the Arabic world until the 17th century[1]. Aside from the introduction of the anesthetic opium and cinchona bark as an anti-malarial drug during the 17th century[2], no significant new contributions were made in pharmacology until the start of the 19th century.

The isolation of morphine from opium by Sertürner in 1815 was the first milestone in medicinal chemistry and initiated the discovery of numerous other interesting alkaloïds the following years. Strychnine **I.1** (Caventou & Pelletier, 1818), nicotine **I.2** (Posselt & Reimann, 1828), atropine **I.3** (Geiger & Hess, 1833) and theobromine **I.4** (Woskresenky, 1842) are a few of the most prominent examples[3] (*figure **I.1-A***). Soon, chemists tried to manipulate these compounds chemically to improve their activity and to reduce their side effects. A famous example was the synthesis of acetylsalicylic acid **I.5** derived from salicin **I.6**, marketed in 1899 by Bayer as Aspirin®, and still one of the most popular drugs in the world with an annual sale of about 12 billion tablets[4] (*figure **I.1-B***). A more infamous example was the synthesis of diacetylmorphine **I.8**, released by Bayer in 1898 under the name of Heroin® and initially promoted as being a less addictive substitute for morphine **I.7**.. In 2010, at least 12 million people worldwide were addicted to heroin[5] .

[1] De Vos, P. *J. Ethnopharmacol.* **2010**, *132(1)*, 28-47.
[2] Kaufman, T. S.; Rúveda, E. A. Angew. *Chem. Int. Ed.* **2005,** *44(6),* 854-885.
[3] Huxtable, R. J.; Schwarz, S. K. W. *Mol. Interv.* **2001**, *1(4)*, 189-191.
[4] Vane, J. R.; Bakhle, Y. S.; Botting, R. M. *Annu. Rev. Pharmacol. Toxicol.* **1998**, *38*, 97–120.
[5] UNODC, World Drug Report 2012.

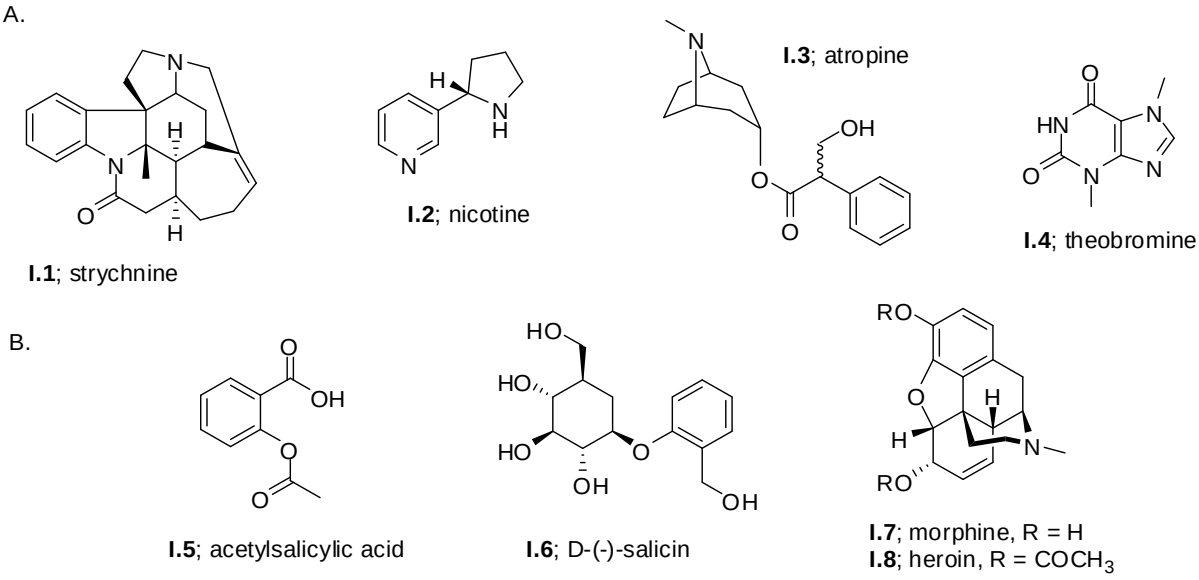

Figure I.1 A. *Prominent examples of isolated alkaloïds in the 19th century* ***B.*** *From D-(-)-salicin to aspirin, from morphine tot heroin*

A second turning point was Wöhler's synthesis of ureum in 1828, refuting the theory of vitalism, which proved to chemists that they could synthesize any organic compound without the help of Nature. In this new perspective, Perkin tried to synthesize quinine and serendipitously discovered the first synthetic dye mauveine in 1856[6]. This compound was the start of industrial chemistry and led to the invention of numerous new dyes[7]. These dyes where not exclusively used in the textile industry, but also in pathology to stain biological tissues *in vivo*. Soon, Ehrlich noticed that some dyes could selectively stain pathogens next to the host tissue and launched the concept of *chemoreceptors*, unique cell structures in each organism capable of binding only specific chemicals. With this idea in mind, Ehrlich thought of synthesizing a chemical compound, a so called *magic bullet*, that selectively targeted the pathogen without harming the host[8]. In 1909, after synthesizing and testing hundreds of organoarsenic compounds based on arsenilic acid **I.9** (*figure **I.2***), Ehrlich and Hata eventually discovered the compound arsphenamine **I.10**[9] as a cure for syphilis[10] (*Treponema pallidum)*. This was the first time that a new drug was found by systematically synthesizing compounds based on a lead compound and this fact can therefore be considered as the real birth of medicinal chemistry. Arsphenamine was launched by Hoechst in 1910 as Salvarsan® and became the first blockbuster drug.

Ehrlich's observations that dyes could be used as antibacterials[11] was picked up by many companies and led to the discovery of other important drugs. Sulfamidochrysoidine **I.11** (*figure **I.2***) for example, an azo-dye containing a sulfonamide moiety, was the first strong antibiotic and led to the invention of numerous so called *sulfa-drugs*[12]. It's discovery delivered Domagk the Nobel Prize for Medicine in 1939.

[6] Perkin, W. H. *Proc. R. Soc.* **1863**, *12*, 713-715.
[7] Zollinger, H. (2003) Introduction. In *Color Chemistry: Synthesis, Properties, and Applications of Organic Dyes and Pigments* (3rd ed., 1-14). Weinheim, Germany: Wiley-VCH.
[8] Drews, J. *Science* **2000**, *287(5460)*, 1960-1964.
[9] Recently, the structure of Salvarsan has been corrected as being a mixture of cyclic arsenic products.
[10] Yarnell, A. *Chem. Eng. News* **2005**, *83(25)*, 116.
[11] Guttmann, P.; Ehrlich, P. *Berl. Klin. Wochenschr.* **1891**, *39*, 903-955.
[12] Domagk, G. *Deutch. Med. Wochenschr.* **1935**, *61*, 250-253.

Another example is methylene blue **I.12**, which was used as a lead for the discovery of chloroquine **I.13**[13], a strong anti-malarial drug, and chlorpromazine **I.14** (Thorazine®), a milestone drug in the treatment of schizophrenia[14] (*figure **I.2***).

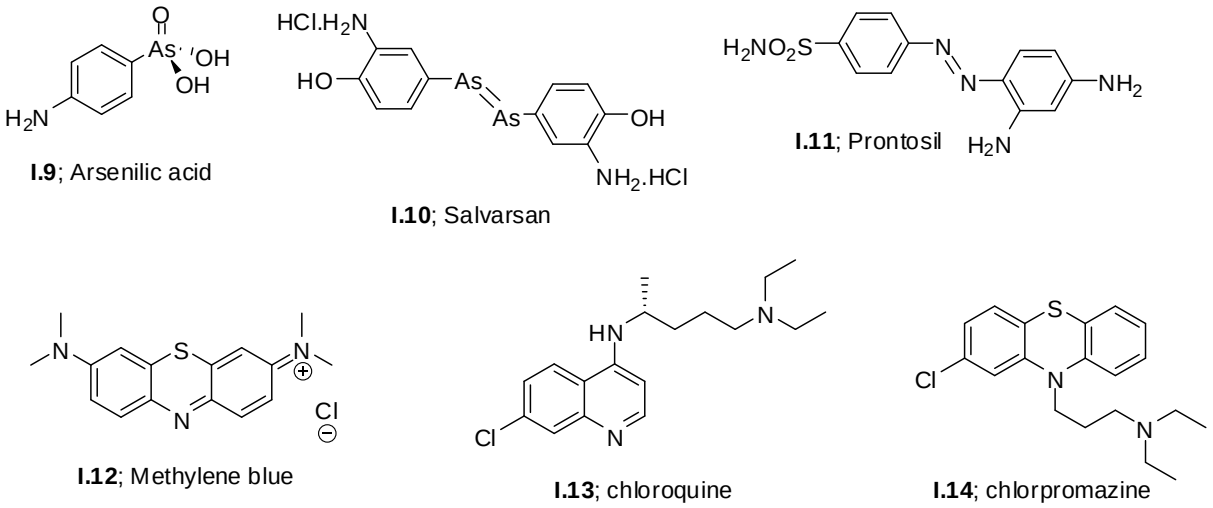

Figure I.2 *A selection of some of the first synthetic drugs*

Another landmark in the history of drug research was the discovery of penicillin **I.15** in 1928 by Fleming[15] (*figure **I.3***). Fleming discovered that bacterial growth in the vicinity of colonies of the mold species *Penicillium notatum* was inhibited. He isolated an active filtrate from the mold and called it penicillin. Because penicillin was not stable enough, Fleming stopped further research in 1935. His research was picked up by Florey and Chain in 1938 who could eventually, with the help of pharmaceutical partners and the US government, industrialize the process of fermenting and extracting the penicillin[16]. Fleming, Florey and Chain were rewarded with the Nobel Prize in Medicine in 1945 for their work on penicillin. Other antibiotics, such as tetracycline **I.16** (1948), cephalosporine **I.17** (1948) and vancomycin (1953) were discovered soon after.

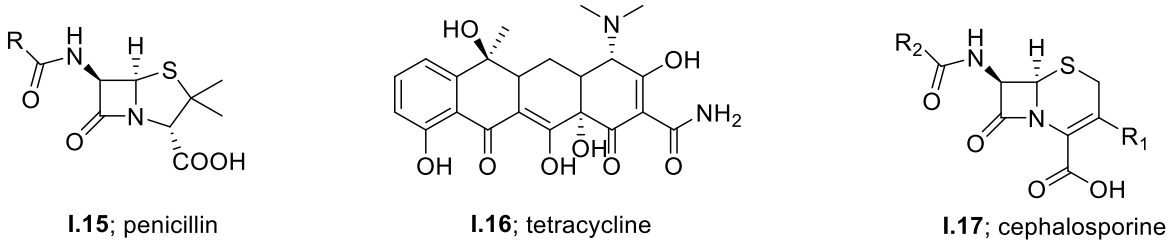

Figure I.3 *Antibiotics*

In the next decades, numerous new drugs were discovered and progress was made in several fields of the drug discovery process[17]. Analysis of new compounds was quickened by the development of organic mass-spectrometry and NMR spectroscopy. The structure of several proteins and receptors

[13] Krafts, K.; Hempelmann, E.; Skórska-Stania, A. *Parasitol. Res.* **2012**, *111(1)*, 1-6.
[14] Ban, T. A. *Neuropsychiatr. Dis. Treat.* **2007**, *3(4)*, 495-500.
[15] Fleming A. *Br. J. Exp. Pathol.* **1929**, *10(31)*, 226–236.
[16] Henry, C. *Chem. Eng. News* **2005**, *83(25)*, 97-97.
[17] Daemmrich, A. A.; Bowden, M. E. *Chem. Eng. News* **2005**, *83(25)*, 28-42.

was elucidated thanks to X-ray crystallography[18] and multi-dimensional NMR[19]. Product purification and separation of complex mixtures became possible by using high pressure chromatographic techniques and capillary electrophoresis. New theoretic concepts such as bioisosterism[20] (Friedman, 1951), the induced-fit model[21] (Koshland, 1958) and QSAR[22] (Hansch, 1962) were introduced and readily picked up by the medicinal chemist. But even with all these innovations, drug discovery remained a time consuming process of trial-and-error.

During the 80's, rational drug design made its entry in the drug discovery process, thanks to the major developments made in the field of computational chemistry. By using techniques such as molecular modeling and docking studies[23], the search for valuable new lead molecules now had a structural base and didn't solely depend on empirical methods anymore. Computer aided drug design proved itself as a useful, complementing tool in the discovery of new leads[24] but it soon became clear that an *in silico* system was still a far from complete model for a real biologic system.

At the end of the eighties, high throughput screening made its way into pharmaceutical research and synthesis suddenly became the bottleneck in the drug discovery process. A new method was necessary to fill up this need for new molecules, it was the birth of combinatorial chemistry.

2. COMBINATORIAL CHEMISTRY

2.1. GENERAL PRINCIPLE

Combinatorial chemistry is the collection of methods to produce large numbers of compounds in a fast and synthetically efficient way in comparison to the traditional organic chemistry. Instead of doing reactions in a stepwise, time-consuming manner (*figure **I.4-A***), reactions are performed simultaneously by systematically combining different building blocks to generate a whole set (*combinatorial library*) of new compounds (*figure **I.4-B***). The number of compounds produced in this way, depends on the number of building blocks and the number of synthetic steps. If A_u building blocks are combined with B_v building blocks in 1 step, A_uB_v compounds can theoretically be generated. Adding a second reaction step using C_w building blocks, already delivers $A_uB_vC_w$ products. In this way, even with a small number of building blocks and by performing only a few reaction steps, already a large number of new compounds can be synthesized. Combinatorial chemistry also works on a relative small scale compared to traditional chemistry, making the process not only fast but also cost reducing. The cost to produce

[18] Adams, M. J.; Blundell, T. L.; Dodson, E. J.; Dodson, G. G.; Vijayan, M.; Baker, E. N.; Harding, M. M.; Hodgkin, D. C.; Rimmer, B.; Sheat, S. *Nature* **1969**, *224*, 491-495.
[19] Kumar, A.; Ernst, R. R.; Wüthrich, K. *BIOCHEM. BIOPHYS. RES. COMM.* **1980**, *95(1)*, 1-6.
[20] Friedman, H. L. *NAS-NRS* **1951**, *206*, p. 295-358.
[21] Koshland, D. E., Jr. *Proc. Natl. Acad. Sci.* **1958**, 44 (2): 98–104.
[22] a) Hansch, C.; Maloney, P. P.; Fujita, T.; Muir, R. M. *Nature* **1962**, *194*, 178-180. b) Hansch, C.; Muir, R. M.; Fujita, T.; Maloney, P. P.; Geiger, C. F.; Streich, M. *J. Am. Chem. Soc.* **1963**, *85*, 2817-2824.
[23] Kuntz, I. D.; Blaney, J. M.; Oatley, S. J.; Langridge, R.; Ferrin, T. E. *J. MOL. BIOL.* **1982**, *161*, 269-288.
[24] Kubinyi, H. J. *Recept. Signal Transduct.* **1999**, *19*, 15-39.

a compound in a combinatorial fashion is predicted to be 600 times less than using traditional chemistry[25].

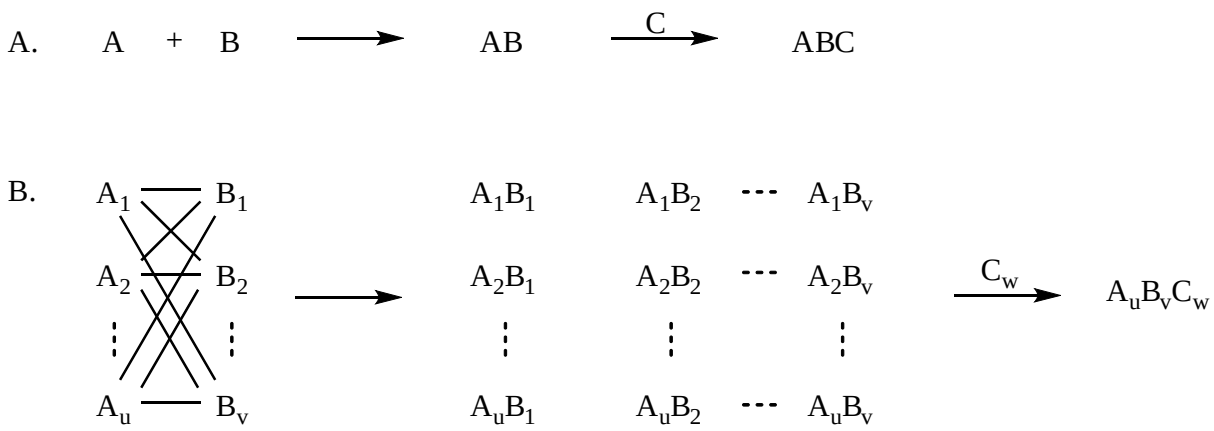

Figure I.4 *Traditional chemistry versus combinatorial chemistry*

2.2. COMBINATORIAL CHEMISTRY USING SOLID PHASE SYNTHESIS TECHNIQUES

Combinatorial chemistry has its roots in peptide synthesis and more specifically in the field of solid phase peptide synthesis. Solid phase synthesis was introduced in 1963 by Merrifield as a new technique to build up peptides[26], using a simple but brilliant strategy. By coupling the first amino acid covalently onto an insoluble polymer resin, the peptide could be built up without purification between each amino acid coupling step. Reagents and solvents could just easily be filtered off and washed away, leaving the peptide untouched onto the solid support. The ease of purification also allowed the use of an excess of reagents, driving the reactions to completion, but the most important advantage was the possibility to automate the whole process. The first automated solid phase procedures and tools for peptide synthesis were introduced by Geysen[27] (Multipin apparatus, 1984) and Houghten[28] ("Tea-bag" approach, 1985).

It was Furka in 1988, who eventually published the first real combinatorial synthesis of peptides using the "portioning-mixing" method[29] (or "split-pool" method). This method exploits the possibilities of combinatorial chemistry maximally, creating gigantic libraries in just a few synthetic steps. The procedure is depicted in *figure **I.5***, and starts with dividing the resin over the different reaction vessels ("split"). After performing the first reaction in each vessel, the resin beads are collected and mixed again ("pool"). By repeating the split and pool step several times, the number of synthesized compounds increases exponentially. The "split-pool"-synthesis finally delivers a library consisting of beads with just one unique product attached to them, a so called "one bead-one compound" library.

[25] Persidis, A. *Nature Biotech.* **1998**, *16*, 691-693.
[26] Merrifield, R. B. *J. Am. Chem. Soc.* **1963**, *85(14)*, 2149-2154.
[27] a) Geysen, H. M.; Meloen, R. H.; Barteling, S. J. *Proc. Natl. Acad. Sci.* **1984**, *81(13)*, 3998-4002. b) Geysen, H. M.; Barteling, S. J.; Meloen, R. H. *Proc. Natl. Acad. Sci.* **1985**, *82(1)*, 178-182.
[28] Houghten, R. A. *Proc. Natl. Acad. Sci.* **1985**, *82(15)*, 5131-5135.
[29] Furka, A.; Sebesteyn, F.; Asgedom, M.; Dibo, G. *Int. J. Pept. Protein Res.* **1991**, *37(6)*, 487-493. b) Sebesteyn, F.; Dibo, G.; Kovacs, A.; Furka, A. *Bioorg. Med. Chem. Lett.* **1993**, *3(3)*, 413-418.

Although this method is the most efficient and fast in producing new compounds, screening and identification of the potentially active compounds is usually lengthy and tedious.

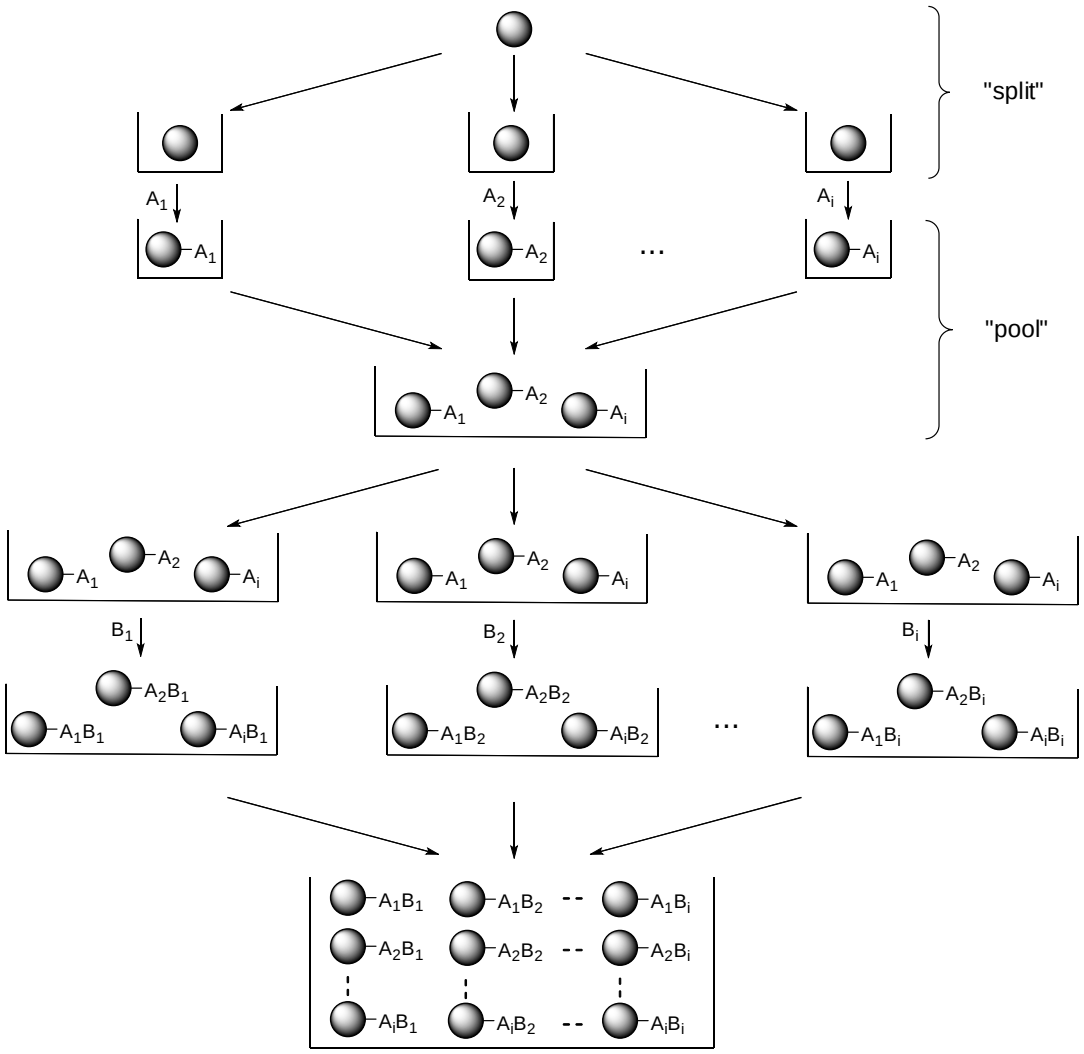

Figure I.5 *"Split-pool"-method*

Another common strategy to build up a combinatorial library is parallel synthesis. In this method, the reactions are performed in spatially separated reaction vessels throughout the whole synthesis (*figure **I.6***). In comparison with "split-pool" methods, parallel synthesis is less reaction efficient and therefore the generated libraries are usually smaller, but each vessel now contains its own unique compound ("one vessel - one compound" principle). Another advantage is that parallel synthesis can be performed both in solution or on solid phase.

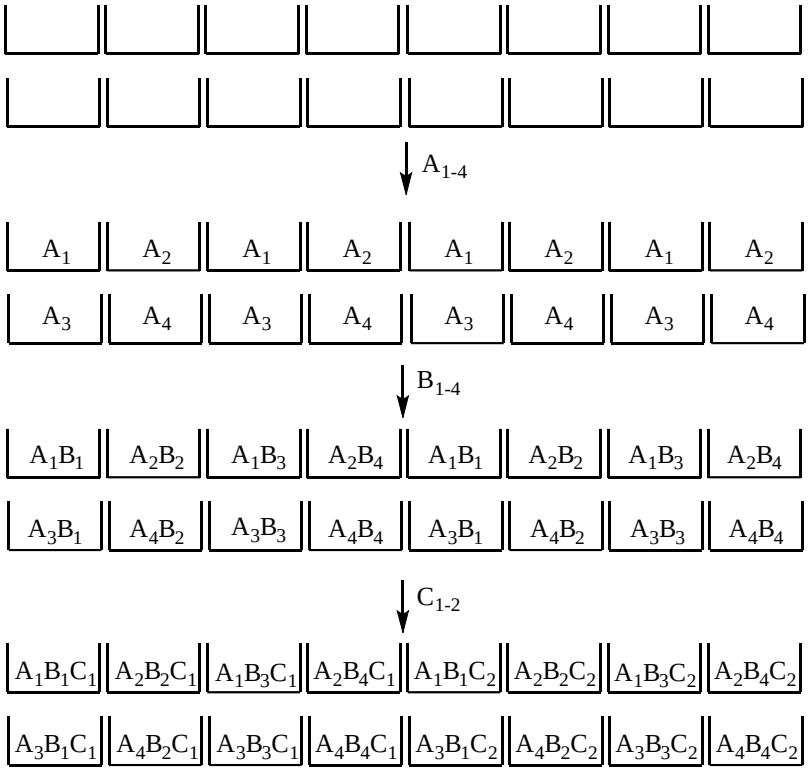

Figure I.6 *Parallel synthesis*

3. SOLID PHASE CHEMISTRY

3.1. RESINS: STRUCTURE AND PROPERTIES

Since Merrifield's introduction of solid phase synthesis, not only new techniques and reactions for solid phase were developed, but the resin itself also underwent an evolution[30]. Where Merrifield originally used lightly crosslinked chloromethylated polystyrene, now a manifold of different solid supports are available each with their own specific properties and applications. Generally, a resin consists of 2 main parts: a polymer backbone and a linker system. Both parts play a crucial role when picking the most suited resin for any given solid phase synthesis and are discussed separately below.

The classic polymer matrix is polystyrene crosslinked with *p*-divinylbenzene (usually 1%), synthesized using suspension polymerization to create nice spherical beads. The size of the beads depends on the application, but is usually around 75-150 μm (100-200 mesh). These polystyrene based polymer beads are popular because they are cheap, chemically inert under various reaction conditions, completely insoluble in common solvents and mechanically stable (e.g. Merrifield resin **I.18**, *figure **I.7***). They display good swelling properties in organic solvents such as THF, dichloromethane and DMF, but swell badly in water, methanol and hexane[31]. Another particular advantage is the ease of modifying the aromatic backbone with a variety of functional groups, which allows the chemist to attach diverse

[30] Merrifield, R. B. (1995). Solid Phase Peptide Synthesis. In Gutte, B. *"Peptides: Synthesis, Structures and Applications"* (pp. 94-170). London: Academic Press Limited.
[31] Santini, R.; Griffith, M. C.; Qi, M. *Tetrahedron Lett.* **1998**, *39(49)*, 8951-8954.

linkers onto the resin. These functional groups are not only present on the surface of the polymer bead, but are evenly distributed throughout the whole bead[32]. When the resin is nicely swollen in an appropriate solvent, the polymer backbone induces no steric hindrance at the reactive sites of the resin. This was illustrated by Sarin *et al.*, who synthesized peptides up to 60 residues on solid phase without loss of efficiency compared to a similar solution phase protocol [33].

The hydrophobic nature of the polystyrene backbone however, could in some cases be disadvantageous and therefore led to the development of polyacrylamide resins[34] (e.g. Sheppard resin **I.19**, *figure **I.7***). The presence of the amide bonds in these resins was believed to provide a better reaction environment for the synthesis of peptides, by counteracting the aggregation of the peptide chains. For the application in continuous flow systems, some polyacrylamide type resins with improved mechanical properties were developed such as Pepsyn K[35], PolyHIPE[36] and Expansin[37].

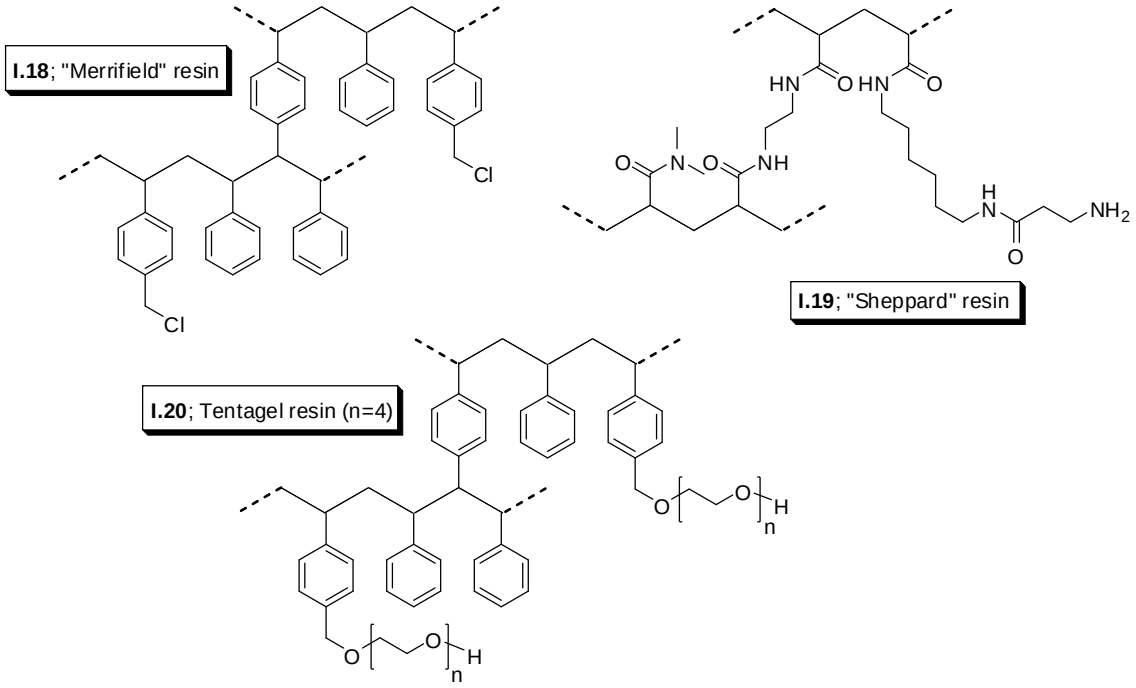

Figure I.7 *Polymer backbones of classic solid phase resins*

Another strategy to improve the hydrophilicity of the polystyrene resins was to graft the polystyrene backbone with polyethyleneglycol chains. This led to the development of different so called PEG

[32] a) Kress, J.; Rose, A.; Frey, J. G.; Brocklesby, W. S.; Ladlow, M.; Mellor, G. W.; Bradley, M. *Chem. Eur. J.* **2001**, *7(18)*, 3880-3883. b) Rademann, J.; Barth, M.; Brock, R.; Egelhaaf, H.-J.; Jung, G. *Chem. Eur. J.* **2001**, *7(18)*, 3884-3889.

[33] Sarin, V. K.; Kent, S. B. H.; Mitchell, A. R.; Merrifield, R. B. *J. Am. Chem. Soc.* **1984**, *106(25)*, 7845-7850.

[34] a) Sheppard, R. C (1973). In *Peptides 1971* (H. Nesvadba, ed.) pp. 111-125. Amsterdam: North-Holland Publ. b) Atherton, E.; Clive, D. L. J.; Sheppard, R. C. *J. Am. Chem. Soc.* **1975**, *97(22)*, 6584-6585. c) Arshady, R.; Atherton, E.; Cleve, D. L. J.; Sheppard, R. C. *J. Chem. Trans., Perkin Trans.* **1981**, *1*, 529-537. d) Kanda, P.; Kennedy, R. C.; Sparrow, J. T. *Int. J. Pept. Protein Res.* **1991**, *38(4)*, 385-391.

[35] Atherton, E.; Brown, E.; Sheppard, R. C.; Rosevear, A. J. *J. Chem. Soc. Chem. Commun.* **1981**, 1151-1152.

[36] Small, P. W.; Sherrington, D. C. *J. Chem. Soc. Chem. Commun.* **1989**, 1589-1591.

[37] Mendre, C.; Sarrade, V; Calas, B. Int. *J. Pept. Protein Res.* **1992**, *39(3)*, 278-284.

resins[38] (e.g. Tentagel **I.20**, *figure **I.7***) with fine to excellent swelling properties in water and methanol. A backside of these resins however is their decreased loading compared to standard polystyrene resins. Other solid supports such as silica[39], glass[40], alumina, phenolic resins[41] or cellulose[42] were also examined but could never rival with the popular polystyrene or polyacrylamide resins.

Of utmost importance for each synthesis performed on a solid support, is the choice of an appropriate linker. The linker is the chemical moiety anchored on the polymer backbone which serves as the point of attachment for the first building block. It is therefore essential that the bond between linker and building block is easily formed, that this bond is not broken during synthesis (*orthogonality*) and that the final product can be cleaved off as such using specific conditions. Due to the variety of linkers that are commercially available today, these cleavage conditions can be very broad: from weakly to strongly acidic, basic, reductive or oxidative, nucleophilic, photolytic,... and are dependent on the synthesis or protection strategy. The most commonly applied conditions for cleavage however are acidic conditions and these are usually based on the formation of a benzyl cation (*figure **I.8***). Depending on the stability of this cation species, the cleavage conditions can be varied from strongly (HF, TFMSA) to mildly acidic (0,1% TFA). The original Merrifield resin **I.18**, bearing no stabilizing substituents, needed to be treated with HF to cleave off the desired peptide. Introduction of a 4-alkyloxybenzylgroup linker (Wang resin **I.21**) however already allowed the use of a concentrated TFA solution to cleave of the desired product[43]. With methoxysubstituents on one[44] (SASRIN resin **I.22**) or both[45] (HAL resin **I.23**) of the *ortho*-positions of the benzylic moeity, even dilute TFA solutions could be used to induce cleavage. Another strategy to stabilize the cation consisted of the introduction of one or two (substituted) phenyl groups on the benzylic positions, resulting respectively in benzhydryl[46] (Rink resin **I.24**) or trityl[47] type resins (trityl resin **I.25** or 2-chlorotrityl **I.26**). Both linkers allow cleavage of the desired products in dilute TFA solutions. More details about linkers, their applications and cleavage conditions will not be discussed further in this work due to the broad scope of this topic, but are extensively reviewed in the literature[48].

[38] Hellerman, H.; Lucas, H.-W.; Maul, J.; Rajasekharan, P. V. N.; Mutter, M. *Makromol. Chem.* **1983**, *184(12)*, 2603-2617.
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[40] Parr, W.; Grohmann, K. *Angew. Chem. Int. Ed.* **1972**, *11(4)*, 314-315.
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[43] Wang, S. S. *J. Am. Chem. Soc.* **1973**, *95(4)*, 1328-1333.
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[45] Albericio, F.; Barany, G. *Tetrahedron Lett.* **1991**, *32(8)*, 1015-1018.
[46] Rink, H. *Tetrahedron Lett.* **1987**; *28(33)*, 3787-3790.
[47] Barlos, K.; Gatos, D.; Kallitsis, J.; Papaphotiu, G.; Sotiriu, P.; Wenging, Y.; Schäfer, W. *Tetrahedron Lett*. **1989**, *30(30)*, 3943-3946.
[48] James, I. W. *Tetrahedron* **1999**, *55(16)*, 4855-4946 and references herein b) Warass, R. Solid-Phase Anchors in Organic Chemistry (1999). In Jung, G., *Combinatorial Chemistry: Synthesis, Analysis, Screening* (pp. 167-228). Weinheim, Germany: Wiley-VCH

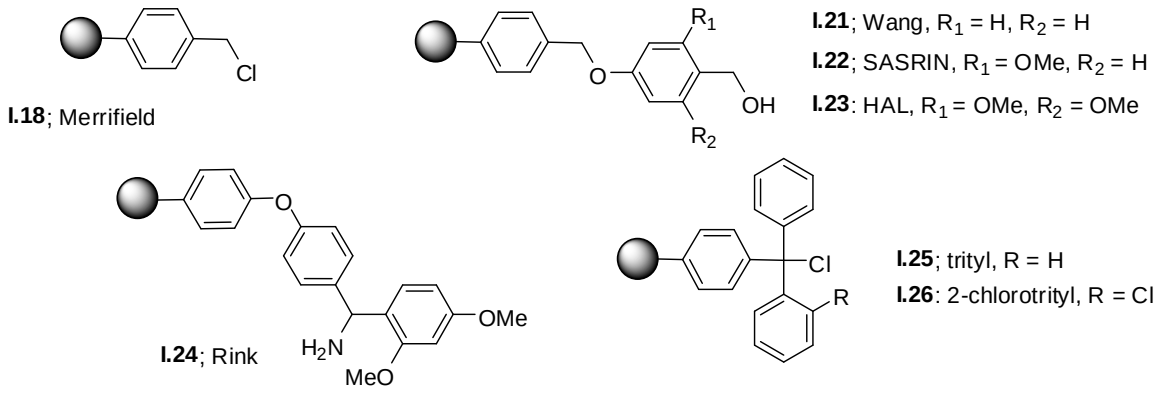

Figure I.8 *Resins with a varying stability towards acids*

4. ANALYSIS ON SOLID PHASE

A disadvantage of solid phase chemistry is that it does not allow an easy follow up of a reaction. Indeed, the reaction substrate is bound covalently onto the solid support, which makes it impossible to monitor reactions directly using routine methods such as TLC, GC-MS or LC-MS. Therefore, new techniques were developed or existing methods adapted for the direct or indirect analysis of solid phase reactions. Below, some "on-bead" and "off-bead" techniques are shortly outlined.

4.1. ON-BEAD ANALYSIS

An on-bead quantitative analysis can only be performed using IR[49] or NMR[50] spectroscopy, and in some cases using MALDI[51]. However, these techniques all have their disadvantages, making a quick and accurate analysis usually quite tedious. Analysis applying FT-IR techniques for example requires the appearance or disappearance of a characteristic absorption band in the spectrum related to the transformation of a functional group, to give a useful result. In addition, band overlap with functional groups present on the solid support could also hinder an accurate monitoring of the reaction.

On-bead analysis using classic NMR techniques also has its limitations, mainly due to the insoluble character of the polymer matrix. The inhomogeneous nature of the sample leads to very broad proton signals in ^{1}H spectra, making this type of analysis nearly useless. Solutions are found in ^{13}C gel-phase techniques, but due to the low sensitivity, an acceptable result usually requires an acquisition time of several hours. However, so called Magic Angle Spinning NMR (MAS NMR), almost completely resolves the matrix interference and makes common ^{1}H and ^{13}C NMR analysis possible. A disadvantage of this technique is that it requires specific and expensive equipment such as a MAS probe, thus making MAS NMR not a routine technique which can be performed in every lab.

[49] a) Yan, B.; Fell, J. B.; Kumaravel, G. *J. Org. Chem.* **1996**, *61(21)*, 7467-7472. b) Yan, B.; Kumaravel, G. *Tetrahedron* **1996**, *52(3)*, 843-848. c) Chan, T. Y.; Chen, R.; M. J. Sofia *Tetrahedron Lett.* **1997**, *38(16)*, 2821-2824

[50] a) Gordeev, M. F.; Patel, D. V.; Gordon, E. M. *J. Org. Chem.* **1996**, *61(3)*, 924-928. b) Garigipati, R. S.; Adams, J. L.; Sarkar, S. K. J. Org. Chem. 1996, 61(8), 2911-2914. c) Riedl, R.; Tappe, R.; Berkessel, A. *J. Am. Chem. Soc.* **1998**, *120(35)*, 8994-9000.

[51] Fitzgerald, M. C.; Harris, K.; Shevlin, C. G.; Siuzdak, G.; *Bioorg. Med. Chem. Lett.* **1996**, *6(8)*, 979-982.

An alternative for these quantitative analysis techniques are the so called color tests. Although these color tests will only deliver a qualitative result, they are quite popular because they are fast, cheap and consume only tiny amounts of product. These tests are based on the derivatization of residual functional groups on the solid support with specific coloring agents. Depending on the (intensity of the) color of the resin beads, a qualitative indication about the amount of free functionalities is obtained. Most color tests have been developed for the determination of free amine groups[52], but there are also color tests designed for other functional groups such as alcohols[53], thiols[54], aldehydes[55] and carboxylic acids[56]. A short overview of the tests applied during this research is depicted in *figure **I.9***.

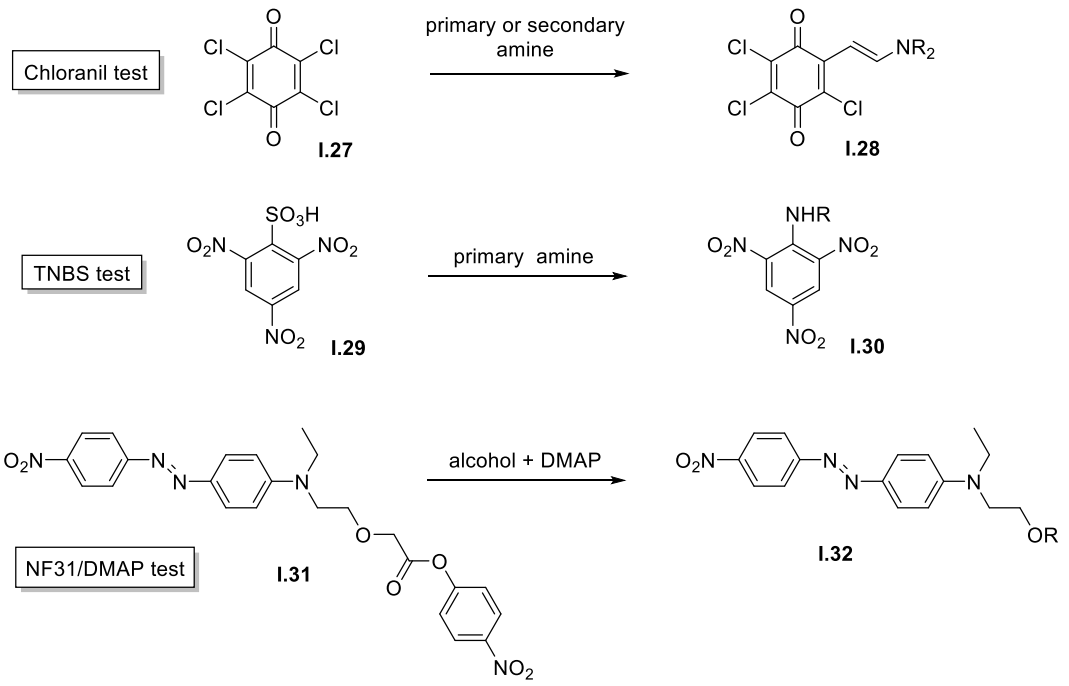

Figure I.9 *Short overview of the color tests applied during this research*

[52] a) Kaiser, E.; Colescott, R. L.; Bossinger, C. D.; Cook, P. I. *Anal. Biochem.* **1970**, *34*, 595-598. b) Sarin, V. K.; Kent, S. B. H.; Tam, J. P.; Merrifield, R. B. *Anal. Biochem.* **1981**, *117*, 147-157. c) Hancock, W. S.; Battersby, J. E. *Anal. Biochem.* **1976**, *71*, 260-264. d) Krchnak, V.; Vagner, J.; Safar, P.; Lebl, M. *Collect. Czech. Chem. Commun.* **1988**, *53*, 2542-2548. e) Reddy, M. P.; Voelker, P. J. *Int. J. Peptide Protein Res.* **1988**, *31*, 345-348. f) Vojkovsky, T. Pept. Res. 1995, 8(4), 236-237. g) Madder, A.; Farcy, N.; Hosten, N. G. C.; De Muynck, H.; De Clercq, P. J.; Barry, J.; Davis, A. P. *Eur. J. Org. Chem.* **1999**, 2787-2791. h) Mařík, J.; Song, A.; Lam, K. S. *Tetrahedron Lett.* **2003**, *44(23)*, 4319-4320. i) Blackburn, C. *Tetrahedron Lett.* **2005**, *46(9)*, 1405-1409. j) Claerhout, S.; Ermolat'ev, D. S.; Van der Eycken, E. V. *J. Comb. Chem.* **2008**, *10(4)*, 580-585.

[53] a) Kuisle, O.; Lolo, M.; Quiñoá, E.; Riguera, R. *Tetrahedron* **1999**, *55(51)*, 14807-14812. b) Attardi, M. E.; Falchi, A.; Taddei, M. *Tetrahedron Lett.* **2000**, *41(38)*, 7395-7399. c) Attardi, M. E.; Taddei, M. *Tetrahedron Lett.* **2001**, *42(15)*, 2927. d) Burkett, B. A.; Brown, R. C. D.; Meloni, M. M. *Tetrahedron Lett.* **2001**, *42(33)*, 5773-5775. e) Caroen, J.; Van der Eycken, J. *Tetrahedron Lett.* **2009**, *50(1)*, 41-44

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[55] a) Cournoyer, J. J.; Kshirsagar, T.; Fantauzzi, P. P.; Figliozzi, G. M.; Makdessian, T.; Yan, B. *J. Comb. Chem* **2002**, *4(2)*, 120-124. b) Shannon, S. K.; Barany, G. *J. Comb. Chem.* **2004**, *6(2)*, 165-170 c) Vázquez, J.; Albericio, F. *Tetrahedron Lett.* **2001**, *42(38)*, 6691-6693.

[56] Attardi, M. E.; Porcu, G.; Taddei, M. *Tetrahedron Lett.* **2000**, *41(38)*, 7391-7394.

4.2. OFF-BEAD ANALYSIS

4.2.1. 9-FLUORENYLMETHOXYCARBONYL TEST (FMOC TEST)

A more frequently used method for quantitative measurements of coupling efficiencies is Fmoc UV-quantification. This method, developed by Sheppard[57], is therefore only applicable when using a Fmoc-based synthetic strategy. It is based upon the formation of the chromophore dibenzofulvene-piperidine adduct **I.35** after base induced elimination of the Fmoc-protecting group with piperidine (*figure **I.10***).

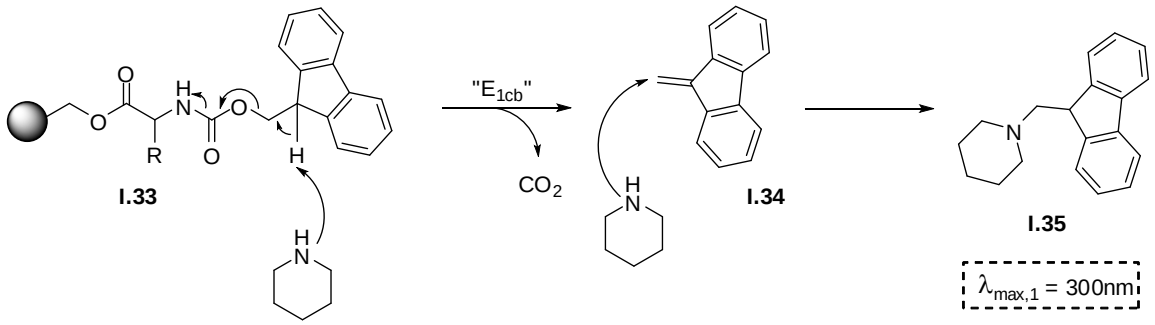


Figure I.10 *Fmoc-deprotection mechanism and piperidine-dibenzofulvene adduct formation*

By measuring the absorption at 300 nm[58] ($\lambda_{max,1}$, *figure **I.11***), the concentration of this adduct can be determined using the Lambert-Beer equation:

$$A = \varepsilon.l.c$$

In which A = absorption, ε = molar extinction coefficient, l = path length, c = molar concentration

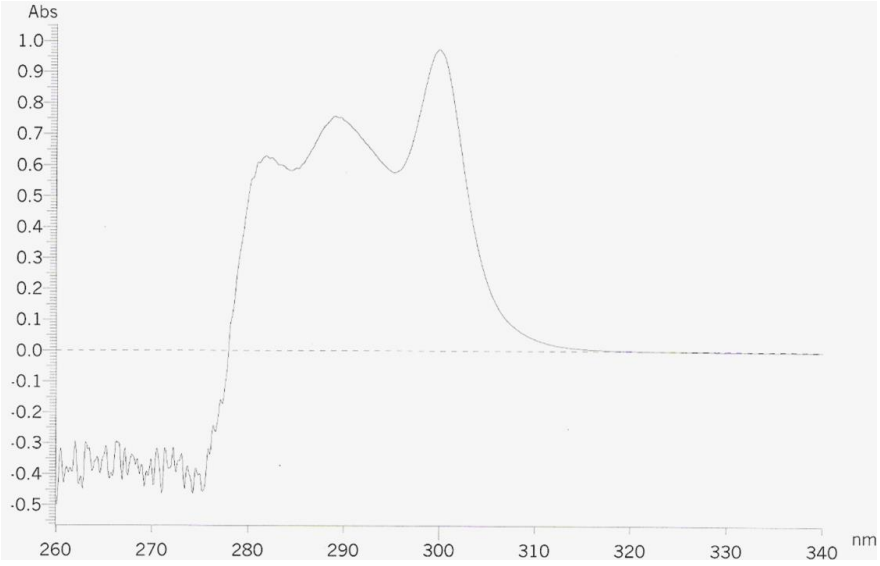


Figure I.11 *UV spectrum of a solution containing the dibenzofulvene-piperdine adduct*

[57] Atherton, E.; Sheppard, R. C. (1989). In *Solid Phase Peptide Synthesis: A Practical Approach* (pp. 1-203). Oxford, England: IRL Press.

[58] The absorbance can also be measured at $\lambda_{max,2}$ = 290 nm.

The extinction coefficient has been experimentally determined in our lab by Caroen and is 8351,8 $M^{-1}cm^{-1}$ for concentrations between 0 en 0.16 mM. However, because of inconveniences concerning the ordering of piperidine, Hachmann suggested the use of 4-methylpiperidine as a suitable replacement[59] because of its similar properties. From then on, this alternative reagent was applied as the standard deprotection reagent in our lab. Practically, the $\lambda_{max,1}$ of the adduct remained at 300 nm, but the extinction coefficient was different and had to be recalculated for the 4-methylpiperidine-dibenzofulvene adduct. The extinction coefficient for this adduct was also determined experimentally by Caroen and is 8358.5 $M^{-1}cm^{-1}$ for concentrations between 0 en 0.16 mM.

This same technique can also be used for the determination of fluorenylmethyl protected esters[60] instead of Fmoc protected amines. Indeed, the Fm-ester cleaves almost as fast as its carbamate analog in the presence of (4-methyl)piperidine and forms the same adduct[61]. The same standard protocol as applied in the Fmoc UV-quantification can therefore be used in the case of Fm-esters.

Other methods based on the release of chromophoric groups are the dimethoxytrityl test (DMT test) for alcohols, the nitrophenyl isothiocyanate-O-trityl (NPIT test), the 1,1-dioxobenzo[b]-thiophen-2-ylmethyloxycarbonyl (Bsmoc test) and the *o*-nitrobenzenesulfonyl chloride test (*o*-NBS test) for amines[62].

4.2.2. SEPARATION TECHNIQUES COUPLED WITH MASS SPECTROMETRY

By far the most interesting analytical techniques for monitoring reactions or identifying compound libraries are the classic separation techniques coupled with mass spectroscopy. These systems deliver a lot of information while they only require a small amount of product compared to the other techniques. This is very convenient, especially for combinatorial synthesis, where the reaction scale is usually very small. The most commonly used separation technique is high pressure liquid chromatography (HPLC), because this has a broad product range, and it is usually combined with a mass spectrometer using electrospray ionization (ESI). This system not only delivers information about the number of compounds that are present in the sample and their relative ratios[63], but it also gives the mass of each of those individual compounds. Other separating systems such as gas chromatography (GC) or capillary electrophoresis (CE), usually coupled with MS, are also regularly used but only for specific applications, such as volatile compounds or peptides. The major drawback of these types of analysis techniques is that the compounds have to be cleaved (chemically) from the resin. In this way, side reactions can occur or undesired byproducts can be formed, influencing the analysis results.

[59] Hachmann, J.; Lebl, M. J. Comb. Chem. 2006, 8, 149.
[60] a) Kessler, H.; Siegmeier, R. *Tetrahedron Lett.* **1983**, *24(3)*, 281-282. b) Bednarek, M. A.; Bodanszky, M. *Int. J. Pept. Prot. Res.* **1983**, *21(2)*, 196-201.
[61] Caroen, J. (2012) *Ontwikkeling van een vastefasesynthesestrategie voor 1,2,3,4,5,6-hexahydro-1,5-benzodiazocine-2,6-dionen voor toepassing in combinatorische bibliotheken* Ph.D. Thesis Ghent University: Belgium.
[62] Kay, C.; Lorthioir, O. E.; Parr, N. J.; Congreve, M.; McKeown, S. C.; Scicinski, J. J. Ley, S. V. *Biotechn. Bioeng.* **2000**, *71(2)*, 110-118.
[63] This is determined by UV spectroscopy, measuring the relative peak areas at 214 nm.

5. COMBINATORIAL CHEMISTRY IN DRUG DISCOVERY

5.1. THE GOLDEN AGE OF COMBINATORIAL CHEMISTRY

Because combinatorial chemistry was introduced as a fast, efficient and cost reducing method to synthesize new compounds, it was almost immediately implemented in the drug discovery process. The initial libraries mainly consisted of (oligo)peptides, because a lot of peptide chemistry on solid phase was already known, and were synthesized using a *mix-split* protocol to maximize the number of obtained compounds. Some biologically active peptides were discovered using this strategy[64] but most of these candidates failed in trials due to their low bioavailability, a common problem with peptides due to their fast degradation in the body. They were soon replaced by structurally related compounds such as peptoids[65], carbamates[66] and ureas[67] which displayed better proteolytic stability and bioavailability.

However, chemistry on solid phase was evolving and a lot of organic reactions in solution had been translated in useful methods for solid phase organic synthesis. This new chemistry was now used to synthesize small molecules on resin, which were pharmaceutically more interesting than oligomeric structures. There was also a trend from split-mix libraries towards parallel synthesized libraries, a consequence of the difficult identification and unreliable screening of mix-split derived libraries. A milestone paper on small molecule synthesis using a solid phase strategy was delivered by Ellman in 1992, describing a general route towards structurally diverse 1,4-benzodiazepines[68]. This work was followed by many others describing library syntheses of other interesting small molecules[69] such as hydantoïns[70], DKP's[71], dihydropyrimidines[72], thiazolidinones[73], etc. However, the global effect of combinatorial chemistry on the drug discovery process was disappointing, with no significant improvement in the number of new lead compounds. The random synthesis of large and complex

[64] a) Owens, R. A.; Gesellchen, P. D.; Houchins, B. J.; DiMarchi, R. D. *Biochem. Biophys. Res.Commun.* **1991**, *181*, 402-408. b) Houghten, R. A.; Pinilla, C.; Blondelle, S. E.; Appel, J. R.; Dooley, C. T.; Cuervo, J. H. *Nature* **1991**, *354*, 84-86. c) Pinilla, C.; Appel, J. R.; Houghten, R. A. *Gene* **1993**, *128*, 71-76.

[65] a) Simon, R. J.; Kania, R. S.; Zuckerman, R. N.; Huebner, V. D.; Jewell, D. A.; Banville, S.; Ng, S.; Wang, L.; Rosenberg, S.; Marlowe, C.; Spellmeyer, D. C.; Tan, R.; Frankel, A. D.; Santi, D. V.; Cohen, F. E.; Bartlett, P. A. *Proc. Natl. Acad. Sci.* **1992**, *89*, 9367-9371. b) Zuckermann, R. N.; Martin, E. J.; Spellmeyer, D. C.; Stauber, G. B.; Shoemaker, K. R.; Kerr, J. M; Figliozzi, G. M.; Goff, D. A.; Siani, M. A.; Simon, R. J.; Banville, S. C.; Brown, E. G.; Wang, L.; Richter, L. S.; Moos, W. H. *J. Med. Chem.* **1994**, *37*, 2678-2685. c) Patel, D. V. (1997) Applications of Combinatorial Technology to Drug Discovery. In Moos, W. H.; Pavia, M. R.; Ellington, A. D.; Kay, B. K. *Annual Reports in Combinatorial Chemistry and Molecular Diversity* (Ed. 1, pp. 78-89). Leiden, Netherlands: ESCOM and references herein.

[66] Cho, C. Y.; Moran, E. J.; Cherry, S. R.; Stephans, J. C.; Fodor, S. P.; Adams, C. L.; Sundaram, A.; Jacobs, J. W.; Schultz, P. G. *Science*, **1993**, *261(5126)*, 1303-1305.

[67] Hutchins, S. M.; Chapman, K. T. *Tetrahedron Lett.* **1994**, *35(24)*, 4055-4058.

[68] Bunin, B. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1992**, *114*, 10997-10998.

[69] An overview of small molecule library synthesis during that period is given in these reviews: a) Dinesh, V. P.; Gordon, E. M. *Drug Discov. Today* **1996**, *1(4)*, 134-144. b) Dolle, R. E. *Mol. Div.* **1997**, *3*, 199-233.

[70] Dewitt, S. H.; Kiely, J. S.; Stankovic, C. J.; Schroeder, M. C.; Reynolds Cody, D. M.; Pavia, M. R. *Proc. Natl. Acad. Sci.* **1993**, *90*, 6909-6913.

[71] Gordon, D. W.; Steele, J. *Bioorg. Med. Chem. Lett.* **1995**,*5*,47-50.

[72] Wipf, P.; Cunningham, A. *Tetrahedron Lett.* **1995**, *36*, 7819-7822.

[73] Look, G. C.; Schullek, J. R.; Hohnes, C. E.; Chinn, J. E.; Gordon, E. M.; Gallop, M. A. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 707-712.

libraries seemed not to be the right approach, the use of combinatorial chemistry had to be re-evaluated.

5.2. THE POST-LIPINSKI ERA

5.2.1. THE INTRODUCTION OF DRUG-LIKENESS

It was clear that focusing on the number of synthesized compounds was not the right strategy to find new leads. More attention had to be paid to library design, a qualitative instead of a quantitative approach, and on the pharmacokinetics of the synthesized molecules. Absorption, distribution, metabolism, excretion and toxicity (so called *ADME-Tox*) were issues that had to be taken into consideration, to lower the attrition rates in (pre)clinical trials. This problem was first tackled by Lipinski, who evaluated the pharmacokinetic properties of 2245 drugs that entered phase II clinical trials[74]. This resulted in a set of 4 physicochemical parameters, associated with aqueous solubility and membrane permeability, which were met by most of the drugs:

1. A molecular weight M_w <500
2. A calculated logarithm of the octanol-water partition coefficient cLog P < 5
3. The number of proton donors <5 (expressed as the sum of OH and NH)
4. The number of proton acceptors <10 (expressed as the sum of O and N)

These restrictions were defined as the 'rule of 5' ('Ro5') and violations of 2 or more of these rules had to be avoided when designing orally available drugs[75]. This 'Rule of 5' was quickly implemented in almost every drug discovery program as an early filter for 'drug-likeness' and proved very valuable ('fail fast, fail cheap'). A lot of other informative studies comparing huge datasets on physical properties of drugs followed, searching for molecular descriptors that could further refine the filter of "drug-likeness". It was found for example that criteria such as polar surface area (PSA) or the number of rotable bonds (associated with molecular rigidity) were important in the design of new drugs. Molecules with a PSA lower than 120 $Å^2$ or containing less than 7 rotable bonds, proved to have an increased oral bioavailability[76]. Another molecular feature which should be taken in consideration when designing drugs is the presence of certain promiscuous functionalities. Some functionalities are metabolically unstable, give rise to false positives in screening or cause toxicity problems and should therefore be avoided in most cases[77].

In lead discovery however, this concept of 'drug-likeness' is not applicable because leads have a significant different pharmacokinetic profile than their future drugs. Indeed, when a lead molecule is

[74] Lipinski, C. A.; Lombardo, F.; Dominy, B. W.; Feeny, P. J. *Adv. Drug Delivery Rev.* **1997**, *23*, 3-25.
[75] The 'Ro5' is only applicable on drugs which are not associated with active transport mechanisms in the body. Some therapeutic classes of compounds also tend to fall outside the Lipinski box such as antibiotics, antifungals and cardiac glycosides.
[76] a) Palm, K.; Stenber, P.; Luthman, K.; Artursson, P. *Pharm. Res.* **1997**, *14*, 568-571. b) Clark, D. E. J. *Pharm. Sci.* **1999**, *88*, 807-814. c) Veber, D. F.; Johnson, S. R.; Cheng, H.-Y.; Smith, B. R..; Ward, K. W.; Kopple, K. D. *J. Med. Chem.* **2002**, *45(12)*, 2615-2623.
[77] a) Polinsky, A. (2003) High-Speed Chemistry Libraries: Assessment of drug-likeness. In Wermuth, C. G. *The Practice of Medicinal Chemistry* (2nd ed. , pp. 147-158). London: Academic Press. b) Rishton, G. M. *Drug Discov. Today* **1997**, *2(9)*, 382-384.

identified, it still needs to undergo a lot of structural transformations before it becomes a useful drug. This difference was first coined by Oprea *et al.* and led to the concept of "lead-likeness"[78]. The authors stated that an ideal lead should have a M_w between 100-350 and a cLogP between 1-3[79], considering the fact that lead optimization tends to increase M_w and lipophilicity. "Lead-like" molecules are not expected to possess high affinity for a target, because their potency can still be tuned during the lead optimization steps. When comparing the properties of a typical combinatorial library for lead discovery during that period with a "lead-like" library, it was clear that the first contained members which were already too heavy and too lipophilic for further optimization (*figure **I.12***).

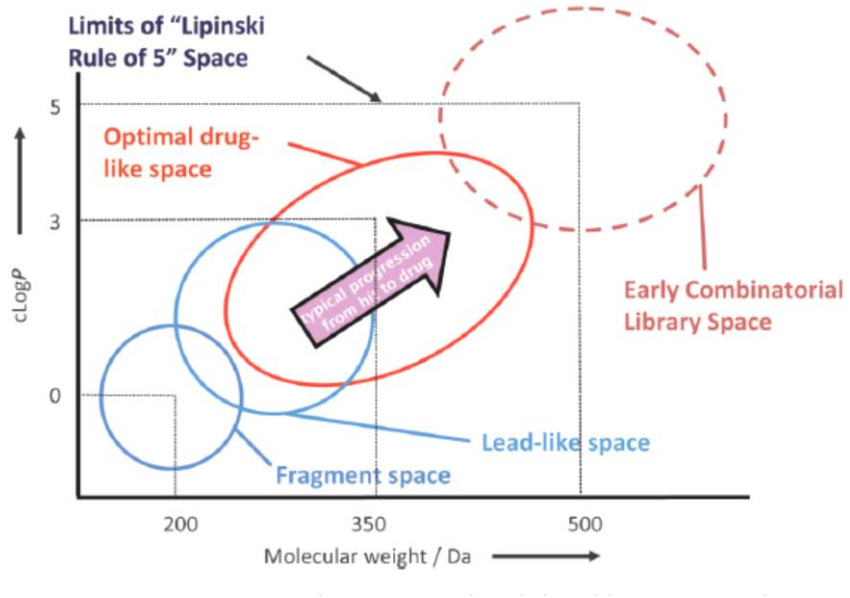


Figure I.12 *Evolution of the lipophilicity and M_w of lead compounds using different approaches (source: Churcher, I. et al.[80])*

Although the concepts of lead-likeness and drug-likeness both improved the overall quality of the combinatorial libraries, there was no significant effect on the output of new molecular entities (NME) after their implementation in drug discovery. This stagnation was also in contrast with the huge increases of R&D investments in the pharmaceutical sector, with costs per NME rising exponentially[81] (*figure **I.13***). Pharmaceutical companies tried to respond to this decline of productivity by mergers and acquisitions and by focusing the research on blockbusters but with no success, on the contrary... These consolidations and the blockbuster business model tempered the innovation, which had always been the backbone of the pharma industry[82]. A new boost in innovation and creativity was then sought in cooperation with academic or public partners. This resulted in new drug discovery strategies such as

[78] Teague, S. J.; Davis, A. M.; Leeson, P. D.; Oprea, T. I. *Angew. Chem. Int. Ed.* **1999**, *38(24)*, 3743-3748.
[79] A so called 'Rule of 3' was devised for fragments: Congreve, M.; Carr, R.; Murray, C.; Jhoti, H. *Drug Discov. Today* **2003**, *8(19)*, 876-877.
[80] Nadin, A.; Hattotuwagama, C.; Churcher, I. *Angew. Chem. Int. Ed.* ***2012****, 51(5),* 1114-1122.
[81] a) Munos, B. *Nature Rev. Drug. Discov.* **2009**, *8(12)*, 959-968. b) Scannell, J. W.; Blanckley, A.; Boldon, H.; Warrington, B. *Nature Rev. Drug Discov.* **2012**, *11(3)*, 191-200.
[82] Bennnani, Y. L. *Drug Discov. Today* **2011**, *16*, 779-792.

Diversity Oriented Synthesis[83], Fragment Based drug design[84] or the Selective Optimization of Side Activities approach[85] (SOSA approach). All these strategy's are treated concisely below.

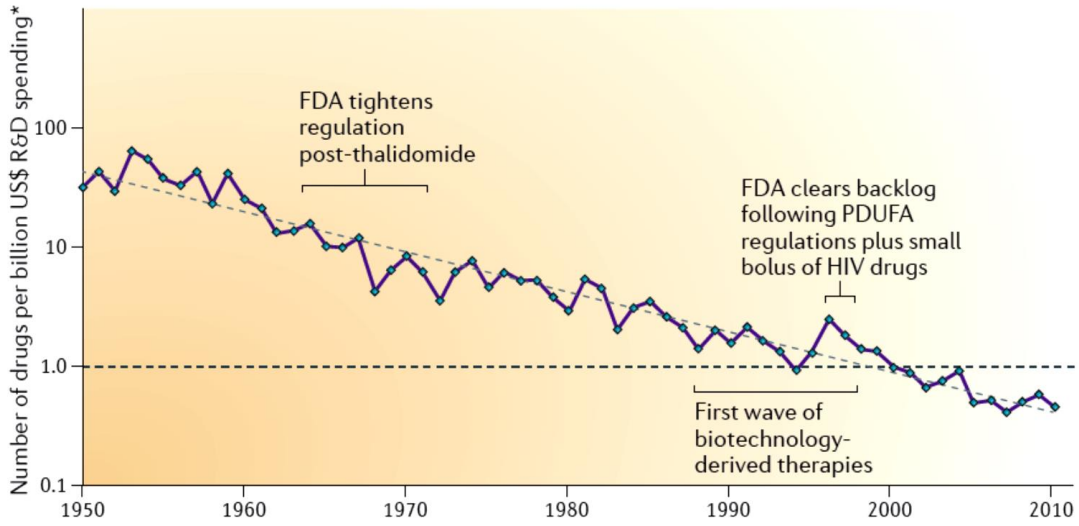


Figure I.13 *Overall trend in R&D efficiency (source: Warrington, B. et al.[86])*

5.2.2. DIVERSITY ORIENTED SYNTHESIS

One of the problems encountered when using a classic combinatorial approach in lead discovery, is the lack of diversity of the resulting library. Indeed, in most cases this approach combines different building blocks, creating a library consisting of only one target scaffold that is differentiated in various positions (a convergent approach)[87]. These libraries also try to avoid the presence of stereocentra and sp^3 carbons, because they tend to complicate the synthetic strategy. In a DOS approach however, the side chains of the (usually chiral) building blocks are specifically chosen to allow several types of reactions with different stereogenic outcome. This has the advantage that multiple scaffolds can be build up using different reaction conditions (a divergent approach), leading to a more diverse and complex library and thus to a more thorough exploration of chemical space (*figure **I.14***).

[83] Schreiber, S. L. *Science* **2000**, *287*, 1964-1969.
[84] Hajduk, P. J.; Greer, J. *Nature Rev. Drug. Discov.* **2007**, *6(3)*, 211-219. b) Rees, D. C.; Congreve, M.; Murray, C. W.; Carr, R. *Nature Rev. Drug. Discov.* **2004**, *3(8)*, 660-672.
[85] a) Wermuth, C. G. *Drug Discov. Today* **2006**, *11*, 160-164. b) Wermuth, C. G. *J. Heterocyclic Chem.* **1998**, *35(5)*, 1091–1100. c) Wermuth, C. G. *Med. Chem. Res.* **2001**, *10*, 431-439.
[86] Scanell, J. W.; Blanckley, A.; Boldon, H.; Warrington, B. *Nature Rev. Drug. Discov*. **2012**, *11(3)*, 191-200.
[87] Spring, D. R. *Org. Biomol. Chem.* **2003**, *1(22)*, 3867-3970.

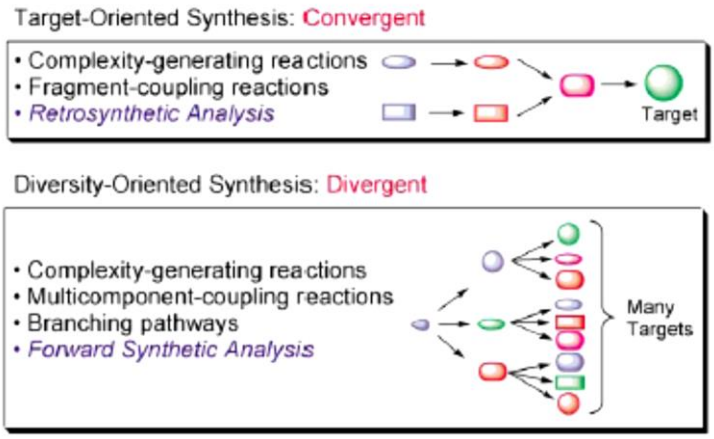


Figure I.14 *Diversity Oriented Synthesis versus Target Oriented Synthesis (source: Spring, D. R.[88])*

In a recent example of this approach, three proline building blocks were synthesized and coupled with each other to deliver several bicyclic and spirocyclic compounds[89]. Another example describes the synthesis of two 8000-membered libraries of 8-membered lactams and sultams starting from a Boc-protected β-hydroxy-γ-amino acid and a PMB-protected alaninol[90].

5.2.3. FRAGMENT BASED DRUG DESIGN

In modern drug research, the classic strategy to identify a new hit for a certain target is to perform a HTS using a huge library of compounds. This usually affords one or more high-affinity hits, which are then processed further to optimize the potency. However, a high-affinity hit derived from a HTS is not always the best starting point for lead-optimization (*figure* ***I.15-B***). Optimizing the potency of such a hit, displaying several low-quality substrate/receptor interactions, usually results in a complex compound with a relatively high molecular weight and thus poor pharmacokinetic profile (*figure* ***I.15-C***). Therefore, it was considered that it would be better to search for small fragments with low-affinity but with high *ligand-efficiency* (*figure* ***I.15-D***) and then link these chemically to find a suitable lead molecule (*figure* ***I.15-E*** *&* ***I.15-F***)[91].

[88] Spring, D. R. *Org. Biomol. Chem.* **2003**, *1(22)*, 3867-3870.
[89] Hung, A. W.; Ramek, A.; Wang, Y.; Kaya, T.; Wilson, A. J.; Clemons, P.A.; Young, D. M. *Proc. Natl. Acad. Sci.* **2011**, *108(17)*, 6799-6804.
[90] Gerard, B.; Duvall, J. R.; Lowe, J. T.; Murillo, T.; Wei, J.; Akella, L. B.; Marcaurelle, L. A. *ACS Combi. Sci.* **2011**, *13(4)*, 365-374.
[91] Carr, R.; Congreve, M.; Murray, C. W.; Rees, D. C. *Drug Discov. Today* **2005**, *10(14)*, 987-992.

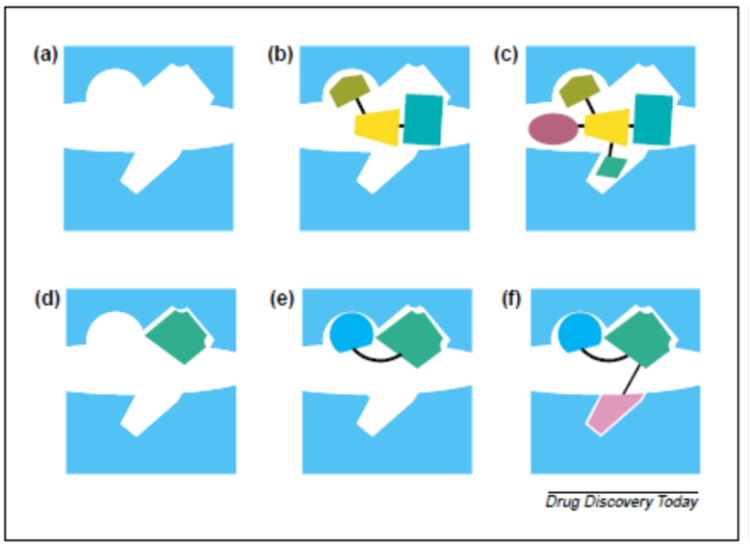


Figure I.15 *Optimization of a high-affinity lead vs. optimization of a ligand-efficient lead (source: Rees, D. C. et al.[92])*

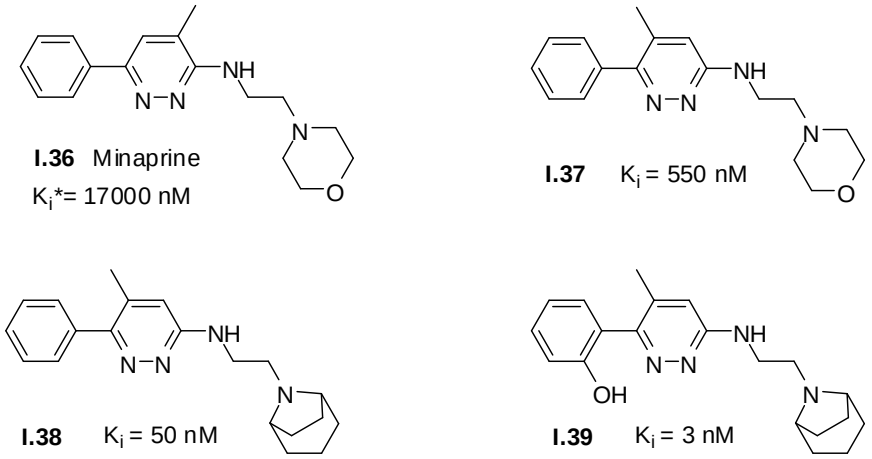
These fragments are typically low functionalized (bi)cyclic compounds with a M_w between 120-250, showing activity for a target in the range of 1mM-30µM. To determine the binding interactions and to optimize the fragment further, fragment based approaches make extensive use of NMR [93] and X-ray crystallography[94]. The first success using a fragment based approach was reported by Hajduk *et al.* in 1997, describing the discovery of a stromelysin inhibitor, by linking an acetohydroxamate fragment with a biaryl fragment[95]. Nowadays, numerous other examples of lead discoveries that made use of fragment based approaches are described in literature[96].

5.2.4. SELECTIVE OPTIMIZATION OF SIDE ACTIVITIES (SOSA)

Some drugs possess, next to their main activity, one or more pharmacological side effects. And while this was first considered as a necessary evil, medicinal chemists quickly realized that this was also an opportunity. Indeed, these molecules could be considered as lead molecules for the optimization of a drug displaying the side effect as principal activity. This selective optimization of side activities (SOSA), has some major advantages in comparison to classic drug research starting from a HTS lead. For example, because the lead molecule is an existing drug, the pharmacokinetic profile has already been optimized. This increases the chance that the molecule with the newly obtained activity, will also contain a good ADME-profile and that there will be less toxicity issues. A molecule that has been used for this purpose is minaprine (*figure* ***I.16***). Minaprine **I.36**, marketed by Sanofi as Cantor®, is a

[92] Carr, R. A. E.; Congreve, M.; Murray, C. W.; Rees, D. C. *Drug Discov. Today* **2005**, *10(14)*, 987-992.
[93] a) Shuker, S. B.; Hajduk, P. J.; Meadows, R. P.; Fesik, S. W. *Science* **1996**, *274*, 1531-1534 b) Meyer, B.; Peters, T. *Angew. Chem. Int. Ed.* **2003**, *42(8)*, 864-890.
[94] Nienaber, V. L.; Richardson, P. L.; Klighofer, V.; Bouska, J. J.; Giranda, V. L.; Greer, J. *Nature Biotech.* **2000**, *18(10)*, 1105-1108.
[95] Hajduk, P. J.; Sheppard, G.; Nettesheim, D. G.; Olejniczak, E. T.; Shuker, S. B.; Meadows, R. P.; Steinman, D. H.; Carrera, G. M., Jr.; Marcotte, P. A.; Severin, J.; Walter, K. Smith, H.; Gubbins, E.; Simmer, R.; Holzman, T. F.; Morgan, D. W.; Davidsen, S. K.; Summers, J. B.; Fesik, S. W. *J. Am. Chem. Soc.* **1997**, *119(25)*, 5818-5827.
[96] a) Rees, D. C.; Congreve, M.; Murray, C. W.; Carr, R. *Nat. Rev. Drug. Disc.* **2004**, *3(8)*, 660-672. b) Hajduk, P. J.; Greer, J. *Nat. Rev. Drug Discov.* **2007**, *6(3)*, 211-219.

pyridazine with antidepressant activity but also with weak affinity towards muscarinic M1-type receptors. By simply adding three structural variations, resulting in structure **I.39**, the activity from minaprine is switched from the dopaminergic to the cholinergic effect[97].



*K_i values measured applying *in vitro* displacement experiments using [3H] pirenzepine, a selective muscarinic M1 antagonist

Figure I.16 *From minaprine, an antidepressant, towards a partial agonist of the muscarinic M1-type receptor (source: Wermuth, C. G. et al.[96])*

5.2.5. PRIVILEGED STRUCTURES

Another interesting concept applied in drug discovery is the use of so called *privileged structures*[98]. The term privileged structures was defined by Evans in 1988 as "a single molecular framework able to provide ligands for diverse receptors". Evans used the term initially to address the 1,4-benzodiazepin-2-one scaffold **I.40**, which proved to be a CCK-A antagonist, but also had affinity for the gastrin and the central benzodiazepine receptor[99]. The reason for this broad activity pattern probably lies in the intrinsic capacity of these scaffolds to interact non-specifically with proteinaceous targets[100]. The side chains of the scaffolds are consequently responsible for the specific interactions, leading to selectivity for a certain target. After this discovery, many other recurring structural motifs were identified in biologically active molecules and categorized as privileged structures[101], such as benzylpiperidine

[97] Wermuth, C. G.; Bourguignon, J-J.; Hoffmann, R.; Boigegrain, R.; Brodin, R.; Kan, J-P.; Soubrié, P. *Bioorg. Med. Chem. Lett.* **1992**, *2(8)*, 833-838.
[98] a) Costantino, L.; Barlocco, D. *Curr. Med. Chem. 2006*, *13*, 65-85. b) Duarte, C. D.; Barreiro, E.; Fraga, C. A. M. *Mini-Rev. Med. Chem.* **2007**, *7(11)*, 1108-1119.
[99] Evans, B. E.; Rittle, K. E.; Bock, M. G.; DiPardo, R. M.; Freidinger, R. M.; Whitter, W. L.; Lundell, G. F.; Veber, D. F.; Anderson, P. S.; Chang, R. S. L.; Lotti, V. J.; Cerino, D. J.; Chen, T.B.; Kling, P. J.; Kunkel, K. A.; Springer, J.P.; Hirschfield, J. *J. Med. Chem.* **1988**, *31(12)*, 2235-2246.
[100] Hajduk, P. J.; Bures, M.; Praestgaard, J.; Fesik, S. W. *J. Med. Chem.* **2000**, *43*, 3443-3447.
[101] A comprehensive list of 46 known privileged scaffolds from both natural as synthetic origin was recently published: Welsch, M. E.; Snyder, S. A.; Stockwell, B. R. *Curr. Opin. Chem. Biol.* **2010**, *14*, 347-361.

I.41[102], indole **I.42**[103], purine **I.43**[104], coumarin **I.44**[105], 6,6'-spiroacetals **I.45**[106], monosaccharides **I.46**[107],... (*figure **I.17***).

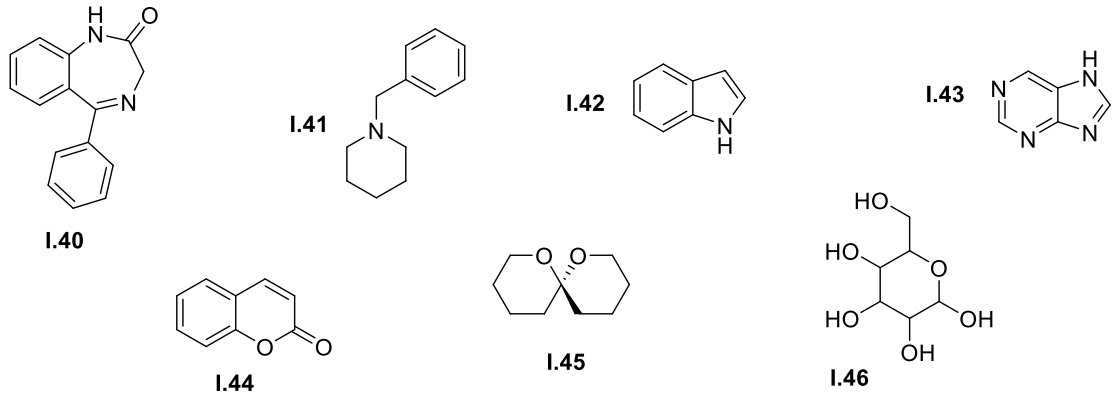


Figure I.17 *Some examples of privileged structures*

Although privileged structures are chemically quite diverse, they tend to share some specific characteristics. Most privileged structures are for example bi/tricyclic heteroatomic small molecules. The preference for these types of systems can probably be linked with their favorable physicochemical properties and rigidity, orienting the side chains in a well-defined chemical space. Owing these qualities, it was anticipated that if such a privileged structure is used as a scaffold in a combinatorial approach, it would lead to the discovery of multiple active molecules for a variety of therapeutic targets. The classic example of thisuarte approach has already been mentioned in the previous section, namely the 1,4-benzodiazepin-2-one synthesis of Ellman *et al.*. The synthesized library consisted of 1680 members and contained three 1,4-benzodiazepin-2-ones showing affinity for three different receptors. Not only the choice for the benzodiazepinone scaffold, but also some other important synthetic decisions made this approach so successful. The choice for a parallel solid phase strategy, the use of a diverse array of commercially available or readily accessible building blocks and the compatibility of this synthesis with different functionalities all contributed to the successful outcome. Some other noteworthy privileged structures that were used in a similar fashion were 2,2-dimethylbenzopyrans[108], prostaglandins[109] and purines[110].

[102] Wieckowska, A.; Wieckowski, K.; Bajda, M; Brus, B.; Salat, K; Czerwinska, P.; Gobec, S.; Filipek, B.; Malawska, B. *Bioorg. Med. Chem.* **2015**, *23(10)*; 2445-2457.
[103] Austin, J. F.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124(7)*, 1172-1173.
[104] a) Boliang, L. *Drug Discov. Today* **2001**, *6(24)*, 1288-1294 b) Chang, Y. T.; Gray, N. S.; Rosania, G. R.; Sutherlin, D. P.; Kwon, S.; Norman, T. C.; Sarohia, R.; Leost, M.; Meijer, L.; Shultz, P. G. *Chem. Biol.* **1999**, *6*, 361-375.
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[106] Arve, L.; Voigt, T.; Waldmann, H. *QSAR Comb. Sci.* **2006**, *25*, 449-456.
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[108] a) Nicolaou, K. C.; Pfefferkorn, J. A.; Roecker, A. J.; Cao, G.-Q.; Barluenga, S.; Mitchell, H. J. *J. Am. Chem. Soc.* **2000**, *122(41)*, 9939-9953. b) Nicolaou, K. C.; Pfefferkorn, J. A.; Mitchell, H. J.; Roecker, A. J.; Barluenga, S.; Cao, G.-Q.; Affleck, R. L.; Lillig, J. E. *J. Am. Chem. Soc.* **2000**, *122(41)*, 9953-9967.
[109] Lee,K. J.; Angulo, A.; Ghazal, P.; Janda, K. D. *Org. Lett.* **1999**, *1*, 1859-186.2
[110] Chang, Y. T.; Gray, N. S.; Rosania, G. R.; Sutherlin, D.P.; Kwon, S.; Norman, T. C.; Sarohia, R.; Leost, M.; Meijer, L.; Shultz, P. G. *Chem. Biol.* **1999**, *6*, 361-375.

6. SULFONAMIDES

The sulfonamide moiety has played a prominent role in medicinal chemistry since its early days. The breakthrough was the discovery that sulfanilamide **I.47** was effective in the battle against bacterial infections, which lead to an explosion of so called "sulfa-drugs" on the market (*figure **I.18a*** and ***I.18b***). Sulfapyridine **I.48**, sulfathiazole **I.49**, sulfadiazine **I.50**, sulfamethoxazole **I.51** and probably the most famous sulfamidochrysoidine **I.11** (Prontosil®) were used intensively until the breakthrough of penicillins as anti-bacterials.

In the search for new anti-bacterials some other sulfonamide containing molecules with a different therapeutic activity were discovered. In 1942, a hypoglycemic effect was observed using IPDT [111], leading to the development of carbutamide **I.52**, a sulfonylureum containing antidiabetic drug[112]. During the same period, the diuretic effect of acetazolamide **I.53** was discovered resulting in famous thiazides such as hydrochlorothiazide **I.54**. Thiazides are also extensively used as anti-hypertensives and led to the development of thiazide-like drugs with the same therapeutic effect such as furosemide **I.55**, clopamide **I.56** and indapamide **I.57**[113]. Next to these main classes of use for sulfonamides, numerous other drugs containing a sulfonamide moiety are known. Celecoxib[114] (COX-2 inhibitor), Tipranavir [115] and Darunavir [116] (protease inhibitors), Probenecid [117] (uricosuric), Argatroban [118] (anticoagulant), Sumatriptan[119] (5HT-agonist), Tamsulosin[120] (α1 receptor antagonist) are some of the most famous examples.

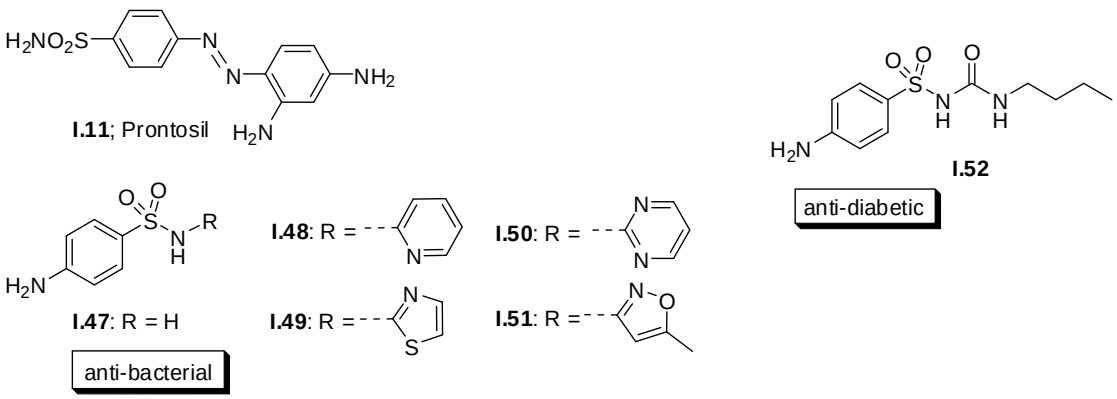

Figure I.18a *Examples of sulfonamide containing drugs*

[111] Janbon, N.; Chaptal, J.; Vedel, A.; Schaap, J. *Montpellier Med.* **1942**, *441*, 21-22.
[112] Kleinsorge, H. *Exp. Clin. Endocrinol. Diabetes* **1998**, *106(2)*, 149-151.
[113] Drews, J. *Science* **2000**, *287*, 1960-1964.
[114] Penning, T. D.; Talley, J. J.; Bertenshaw, S. R.; Carter, J. S.; Collins, P. W.; Docter, S.; Graneto, M. J.; Lee, L. F.; Malecha, J. W.; Miyashiro, J. M.; Rogers, R. S.; Rogier, D. J.; Yu, S. S.; Anderson, G. D.; Burton, E. G.; Cogburn, J. N.; Gregory, S. A.; Koboldt, C. M.; Perkins, W. E.; Seibert, K.; Veenhuizen, A. W.; Zhang, Y. Y.; Isakson, P. C. *J. Med. Chem.* **1997**, *40(9)*, 1347-1365.
[115] Doyon, L.; Tremblay, S.; Bourgon, L.; Wardrop, E.; Cordingley, M. G. *Antiviral Res.* **2005**, *68(1)*, 27-35.
[116] Ghosh, A. K.; Dawson, Z. L.; Mitsuya, H. *Bioorg. Med. Chem.* **2007**, *15(24)*, 7576-7580.
[117] Silverman, W.; Locovei, S.; Dahl, G. *Am. J. Physiol. Cell Physiol.* **2008**, *295(3)*, C761-C767.
[118] Di Nisio, M.; Middeldorp, S.; Büller, H. R. *New Engl. J. Med.* **2005**, *353(10)*, 1028-1040.
[119] Saxena, P.; Ferrari, M. *Cephalagia* **1992**, *12(4)*, 187-196.
[120] Yamada, S.; Tanaka, C.; Kimura, R.; Kawabe, K. *Life Sci.* **1994**, *54(24)*, 1845-1854.

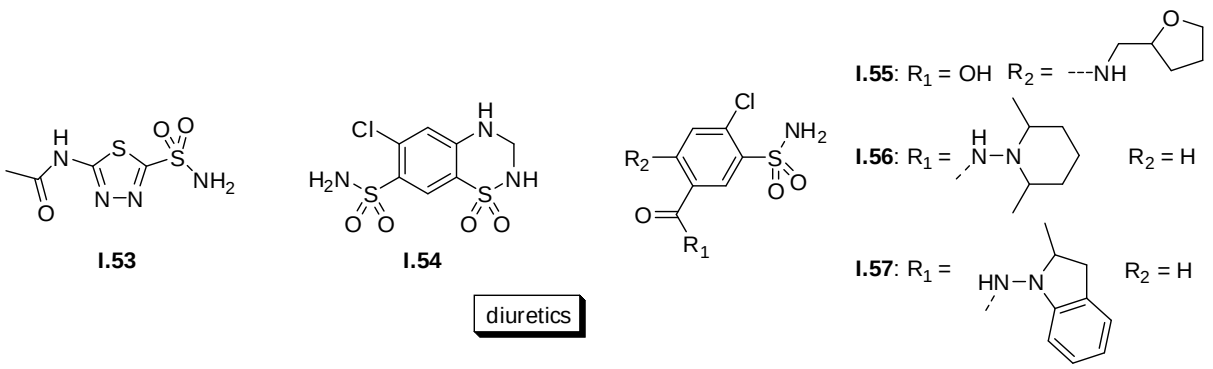

Figure I.18b *Examples of sulfonamide containing drugs*

The sulfonamide moiety is also interesting as a replacement for the classic amide bond. This modification generally results in an increased metabolic stability and thus better bioavailability compared to the original amide compound[121]. These improved properties are a consequence of the geometry of the sulfonamide, which is characterized by a distorted tetrahedral conformation (*figure **I.19-C***). The tetrahedral angle is distorted due to the repulsion of the two oxygen atoms of the sulfoxide, increasing the O=S=O bond angle to 117.5°-120°. This leads to a decrease of the other bond angles to a value lower than 109.5°. This specific configuration is also a good mimic of the tetrahedral transition state of the amide bond during its enzymatic cleavage (*figure **I.19-A*** and ***I.19-B***), making these sulfonamides interesting in the development of protease inhibitors[122].

The length of the S-N bond distance is smaller than a classic S-N bond but larger than a S=N double bond, mainly due to the electrostatic interaction between S and N[123]. Another striking structural property of the sulfonamide is that it retains the C_1^{α}-S bond in gauche conformation compared to the N-C_2^{α} bond and also the lone pair of the nitrogen anti-periplanar towards the C_1^{α}-S bond in a majority of the cases.

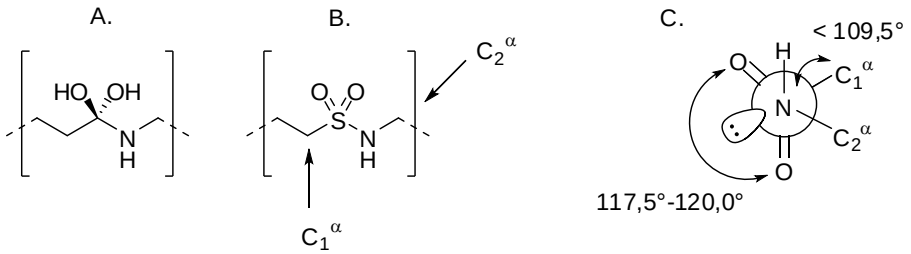

Figure I.19 *Structural properties of sulfonamides **A.** transition state of the hydrolysis of an amide **B.** sulfonamides as structural mimics of the amide hydrolysis transition state **C.** Newman projection of the sulfonamide bond*

The N-H of the sulfonamide is much more acidic (pK_a = 11-12) compared to the classic amide N-H bond (pK_a = 15-16) and proves to be a better hydrogen donor. The hydrogen acceptor capacity of the sulfonyl

[121] Obreza, A.; Gobec, S. *Curr. Med. Chem.* **2004**, *11(24)*, 3263-3278.
[122] Moree, W. J.; van Gent, L. C.; van der Marel, G. A.; Liskamp, R. M. J. *Tetrahedron* **1993**, *49(5)*, 1133-1150.
[123] Bharatam, P. V.; Amita; Gupta, A.; Kaur, D. *Tetrahedron* **2002**, *58(9)*, 1759-1764.

moiety however is very low compared to the amide carbonyl, being even worse than carbamates and esters[124].

[124] Gennari, C.; Gude, M.; Potenza, D.; Piarulli, U. *Chem. Eur. J.* **1998**, *4(10)*, 1924-1931.

7. BENZOTHIADIAZEPINES, THIADIAZEPANES AND BENZOTHIADIAZOCINES AS POTENTIAL PRIVILEGED STRUCTURES

The success of 1,4-benzodiazepin-2-ones as privileged structures led to the synthesis and pharmaceutical evaluation of several structural analogs such as 1,5-benzodiazepin-2-ones **I.58**[125], 1,4-benzodiazepin-2,5-diones **I.59** [126] , 1,4-benzothiazepin-5-ones **I.60** [127] , pyrrolidino[2,1-c]-1,4-benzodiazepin-5,11-ones **I.61**[128] and 5,11-dihydro-benzo[e]pyrido[3,2-b][1,4]diazepin-6-ones **I.62**[129] (*figure **I.20***). Each of these molecules proved to be valuable scaffolds in the search for promising leads, showing biological activity for an array of different targets[130].

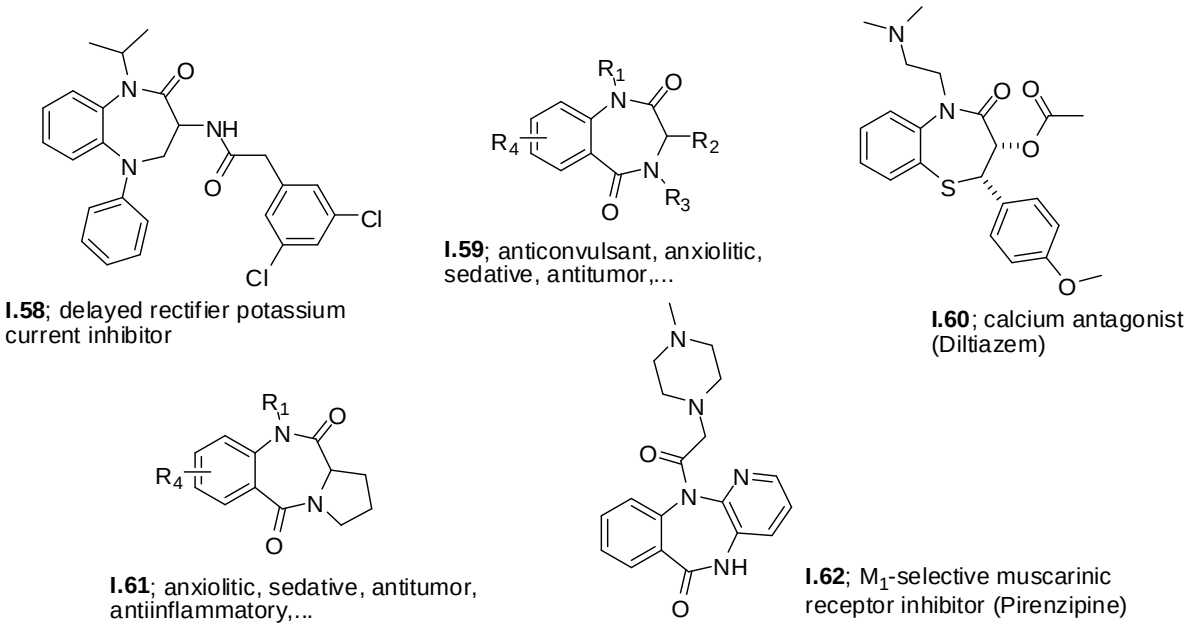

Figure I.20 *Some pharmaceutically active benzodiazepine analogs*

Also the diazepanes, benzodiazepine analogs lacking the fused benzogroup, were investigated and proved to possess various biological activities. For example, they have been described as orexin

[125] a) Herpin, T. F.; Van Kirk, K. G.; Salvino, G. M.; Yu, S. T.; Labaudiniere, R. F. *J. Comb. Chem.* **2000**, *2(5)*, 513-521. b) Zohreh, N.; Alizadeh, A.; Bijanzadeh, H. R.; Zhu, L.-G. *J. Comb. Chem.* **2010**, *12(4)*, 497-502.

[126] a) Keating, T. A.; Armstrong, R. W. *J. Org. Chem.* **1996**, *61(25)*, 8935-8939. b) Hulme, C.; Peng, J.; Tang, S.-Y.; Burns, C. J.; Morize, I.; Labaudiniere, R. J. *J. Org. Chem.* **1998**, *63(22)*, 8021-8023. c) Mayer, J. P.; Zhang, J.; Bjergarde, K.; Lenz, D.; M.; Gaudino, J. *Tetrahedron Lett.* **1996**, *37(45)*, 8081-8084.

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[129] Woolard, F. X.; Paetsch, J.; Ellman, J. A. *J. Org. Chem.* **1997**, *62(18)*, 6102-6103.

[130] Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103(3)*, 893-930.

receptor antagonists **I.63**[131], LFA-1 inhibitors **I.64**[132], chymase inhibitors **I.65**[133] , apoptotic protease-activating factor 1 inhibitors **I.66**[134] and also showed histamine H3[135] and σ1 receptor activity **I.67**[136] (*figure **I.21***).

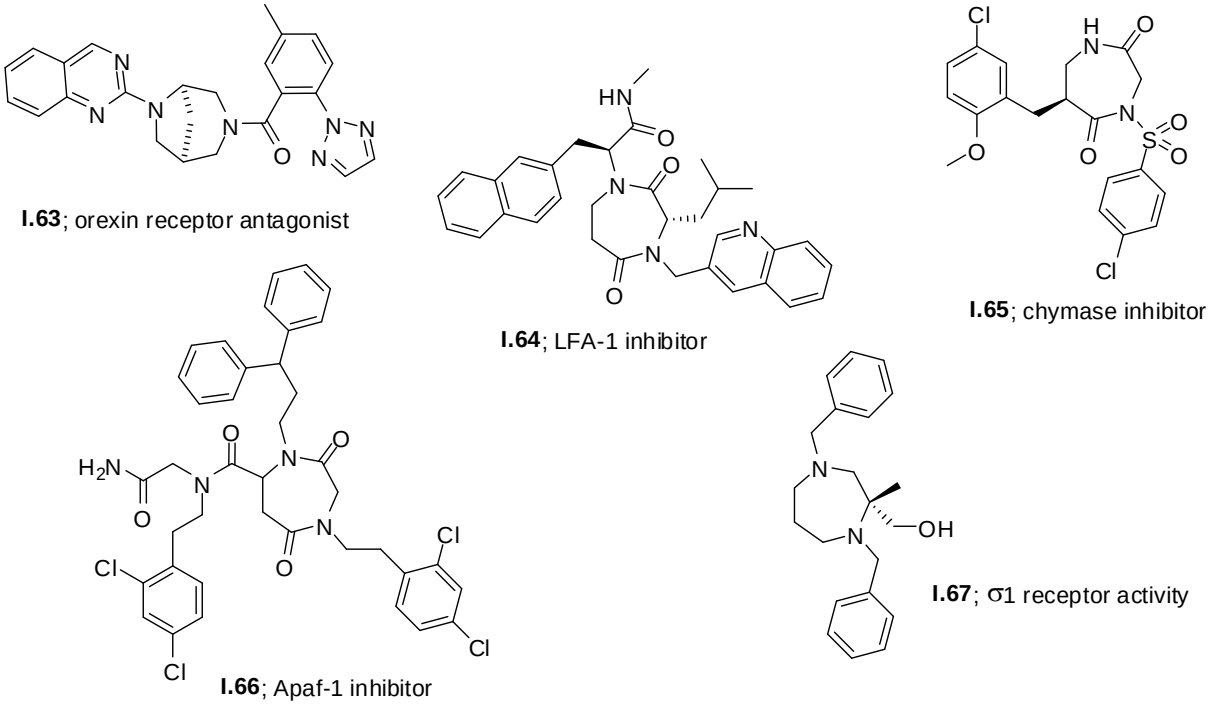

Figure I.21 *Some pharmaceutically active 1,4-diazepines*

We were therefore interested in investigating new or underexplored classes of diazepines, such as the 2,3-dihydro-1,2,5-benzothiadiazepin-4(5*H*)-one-1,1-dioxides **I.68**, the 1,2,5-thiadiazepan-4-one-1,1-dioxides **I.69** and the 3,4-dihydro-2*H*-1,2,6-benzothiadiazocin-5(6*H*)-one-1,1-dioxides **I.70** (*figure **I.22***). In the following sections, a literature overview is given of these three scaffolds.

[131] Coleman, P. J.; Schreier, J. D.; McGaughey, G. B.; Bogusky, M. J.; Cox, C. D.; Hartman, G. D.; Ball, R. G.; Meacham Harrell, C.; Reiss, D. R., Prueksaritanont, T.; Winrow, C. J.; Renger, J. J. *Bioorg. Med. Chem. Lett.* **2010**, *20(7)*, 2311-2315.
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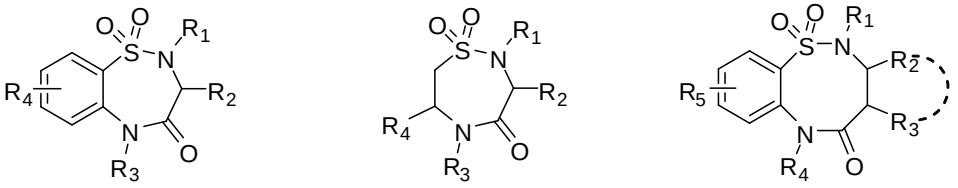
[136] Bedürftig, S.; Wünsch, B. *Eur. J. Med. Chem.* **2009**, *44(2)*, 519-525.



I.68 **I.69** **I.70**

Figure I.22 *Target molecules: the 1,2,5-benzothiadiazepin-4-one-1,1-dioxides* ***I.68****, the 1,2,5-thiadiazepan-4-one-1,1-dioxides* ***I.69*** *and the 1,2,6-benzothiadiazocin-5-one-1,1-dioxides* ***I.70****.*

7.1. 2,3-DIHYDRO-1,2,5-BENZOTHIADIAZEPIN-4(5*H*)-ONE-1,1-DIOXIDES

The 2,3-dihydro-1,2,5-benzothiadiazepin-4(5*H*)-one-1,1-dioxide scaffold **I.68** was first patented in 1965 and consisted of two main building blocks: a substituted 2-nitrobenzenesulfonyl chloride **I.71** and an ester of pipecolic acid **I.72** [137] . First, a pipecolate was coupled with the 2-nitrobenzenesulfonyl chloride, followed by reduction of the nitro moiety and hydrolysis of the ester. Subsequent activation of the carboxylic acid using thionyl chloride, phosphorus trichloride or phosphorus pentachloride, delivered the ring closed product **I.74** (*figure* ***I.23***). The products were patented as diuretics and anti-hypertensives. This patent was directly followed by a second patent by the same author describing the carbonyl reduced analogs, the 2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine-1,1-dioxides[138]. The synthesis was performed in a similar fashion as described in the first patent, only differing in an extra carbonyl reducing step using a suitable reducing agent such as lithium aluminum hydride to obtain the desired final compounds. In 1969 the latter structures were described in a US patent describing their use as depressants, anticonvulsants and hypoglycemic agents[139].

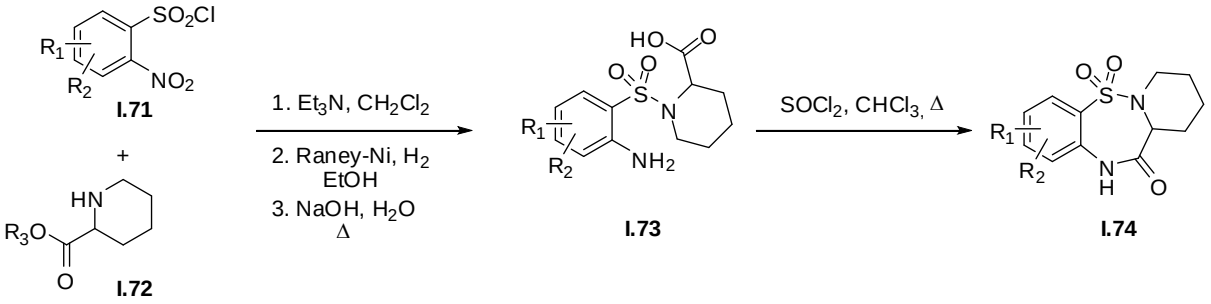


Figure I.23 *Synthesis of the first 2,3-dihydro-1,2,5-benzothiadiazepin-4-one-1,1-dioxide by Pfenninger*

The 1,2,5-benzothiadiazepin-4-one-1,1-dioxide scaffold was again patented in 1991 for its therapeutic use as an antiarrhythmic, local anesthetic and calcium antagonistic agent[140]. The synthesis of the scaffold was conducted using the same strategy as described in the previous patents[141] (*figure* ***I.24***). The side chains on position N_2 and N_5 could be introduced selectively after ring closure using

[137] Pfenninger, H. A. *BE Patent No. 658844 A*, **1965**.
[138] Pfenninger, H. A. *BE Patent No. 658845 A*, **1965**.
[139] Wei, P. H. L.; Bell, S. C. *U.S. Patent No. 3453266*, **1969**.
[140] Ogawa, K.; Matsushita, Y.-I. *PCT int. Appl. WO90/04590*, **1991**.
[141] Ogawa, K.; Matsushita, Y.-I. *Chem. Pharm. Bull.* **1992**, *40(9)*, 2442-2447.

respectively alkyl or benzyl halides in the presence of potassium carbonate and aminoalkyl halides in the presence of sodium hydride, delivering compounds **I.79**. N_5 alkylation with epichlorohydrin in the presence of sodium hydride allowed further derivatization with different amines, leading to the corresponding 3-amino-2-hydroxypropyl analogs **I.81**.

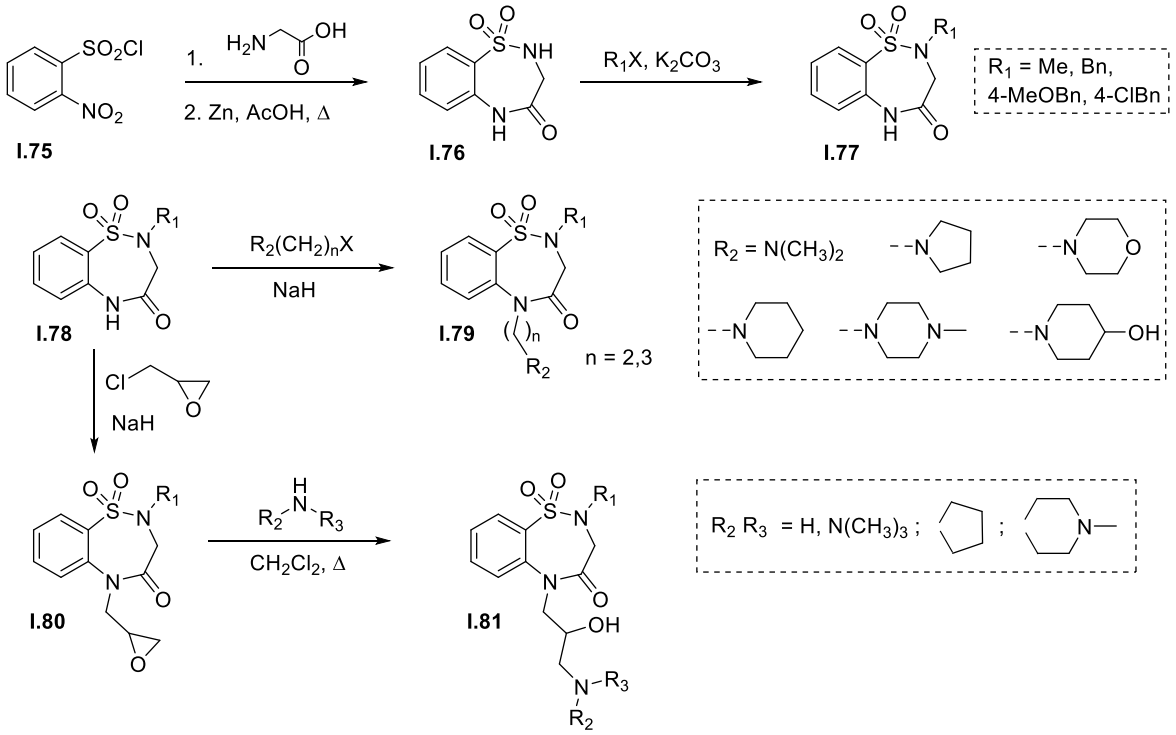


Figure I.24 *Synthesis of 2,3-dihydro-1,2,5-benzothiadiazepin-4-one-1,1-dioxides by Ogawa et al.*

5-Acetoamide analogs **I.83** were synthesized by alkylation of the N_5 position using sodium hydride and a chloroamide reagent (*figure **I.25***). An alternative route was needed to introduce the 4-methylchloroacetylpiperazine building block, starting with the introduction of *t*-butylbromoacetate on the N_5 position. Subsequent acid hydrolysis of the ester followed by coupling of 1-methylpiperazine with DCC eventually afforded the right product **I.86**.

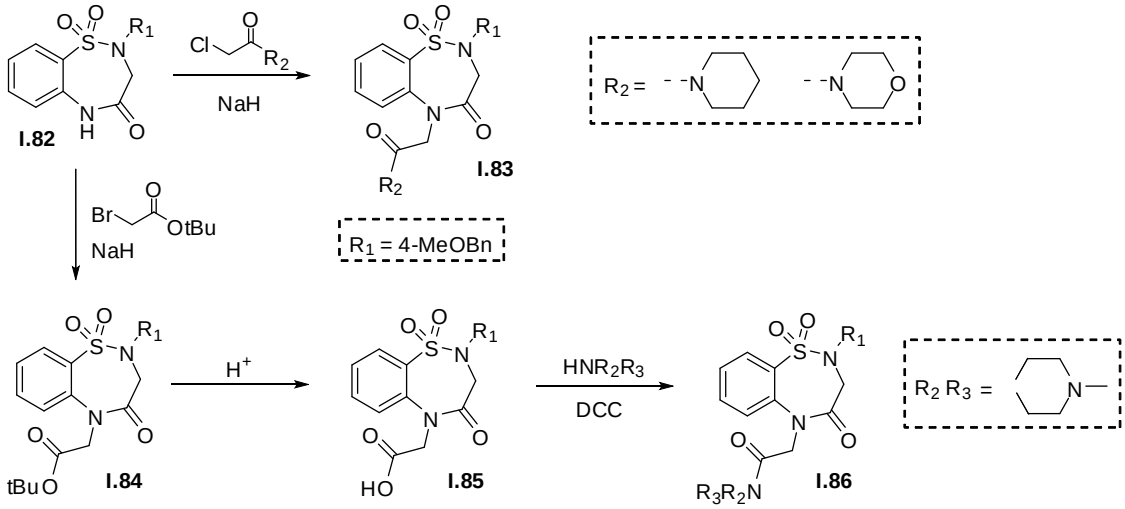
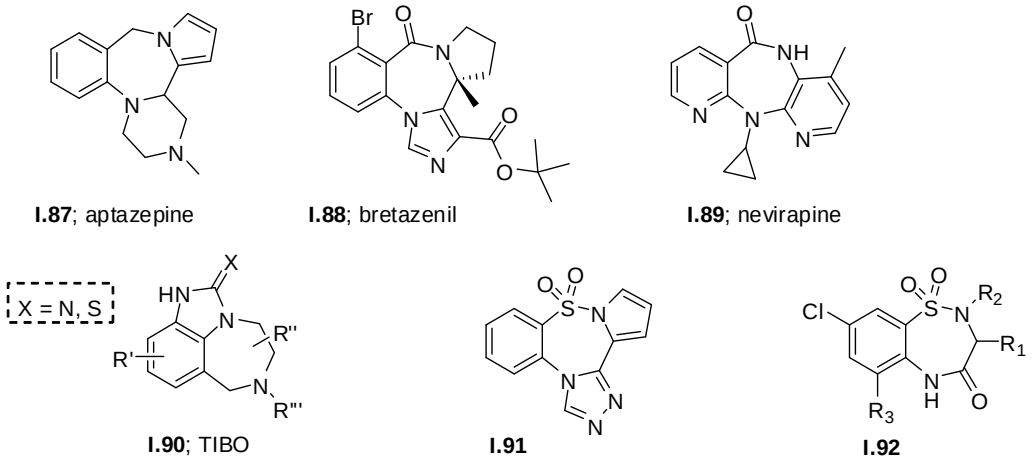


Figure I.25 *Further derivatization of 1,2,5-benzothiadiazepin-4-one-1,1-dioxides by Ogawa et al.*

Further exploration of the benzothiadiazepines was performed by Artico, Silvestri and Stefancich, who delivered synthetic routes towards different analogs of the pyrrolo[1,2-b][1,2,5] benzothiadiazepine-5,5-dioxides **I.91**[142] (*figure **I.26***). These structures displayed structural analogies with the anti-depressant aptazepine **I.87**, the anti-anxiolytic bretazenil **I.88** and NNRTIs such as Nevirapine **I.89** and TIBO **I.90**, and were therefore considered promising candidates for further investigation. One part of the synthesized library consisted of 2,3-dihydro-1,2,5-benzothiadiazepin-4(5*H*)-one-1,1-dioxides **I.92**, of which some members showed anti-HIV-1 activity[143].



I.87; aptazepine **I.88**; bretazenil **I.89**; nevirapine

I.90; TIBO **I.91** **I.92**

Figure I.26 *Pyrrolo[1,2-b][1,2,5]benzothiadiazepine-5,5-dioxides as analogs of pharmaceutically interesting benzodiazepines*

These compounds were synthesized by coupling 5-chloro-2-nitrobenzenesulfonyl chlorides **I.93** with the ethyl esters of glycine or alanine **I.94** (*figure **I.27***). Subsequently, reduction of the nitro moiety was performed using iron in acetic acid followed by hydrolyzing the ethyl esters. Amide bond formation with EDC and DMAP finally yielded the ring closed benzothiadiazepines **I.97**. An extra nitro substituent could be introduced on position 6 by reacting compound **I.98** in concentrated nitric acid.

[142] a) Artico, M.; Silvestri, R.; Stefancich, G. *Synth. Comm.* **1992**, *22(10)*, 1433-1439. b) Silvestri, R.; Artico, M.; Pagnozzi, E.; Stefancich, G. *J. Heterocyclic Chem.* **1994**, *31(4)*, 1033-1036. c) Di Santo, R; Costi, R.; Artico, M. *J. Heterocyclic Chem.* **1996**, *33(6)*, 2019-2023. d) Artico, M.; Silvestri, R.; Pagnozzi, E.; Stefancich, G.; Massa, S.; Loi, A. G.; Putzolu, M.; Corrias, S.; Spiga, M. G.; La Colla, P. *Bioorg. Med. Chem.* **1996**, *4(6)*, 837-850 e) Di Santo, R; Costi, R.; Massa, S.; Artico, M. *Synth. Comm.* **1998**, *28(13)*, 2517-2530. f) Costi, R.; Di Santo, R.; Artico, M. *J. Heterocyclic Chem.* **2002**, *39(1)*, 81-90.

[143] Di Santo, R.; Costi, R.; Artico, M.; Ragno, R.; Lavecchia, A.; Novellino, E.; Gavuzzo, E.; La Torre, F.; Cirilli, R.; Cancio, R.; Maga, G. *ChemMedChem* **2006**, *1(1)*, 82-95.

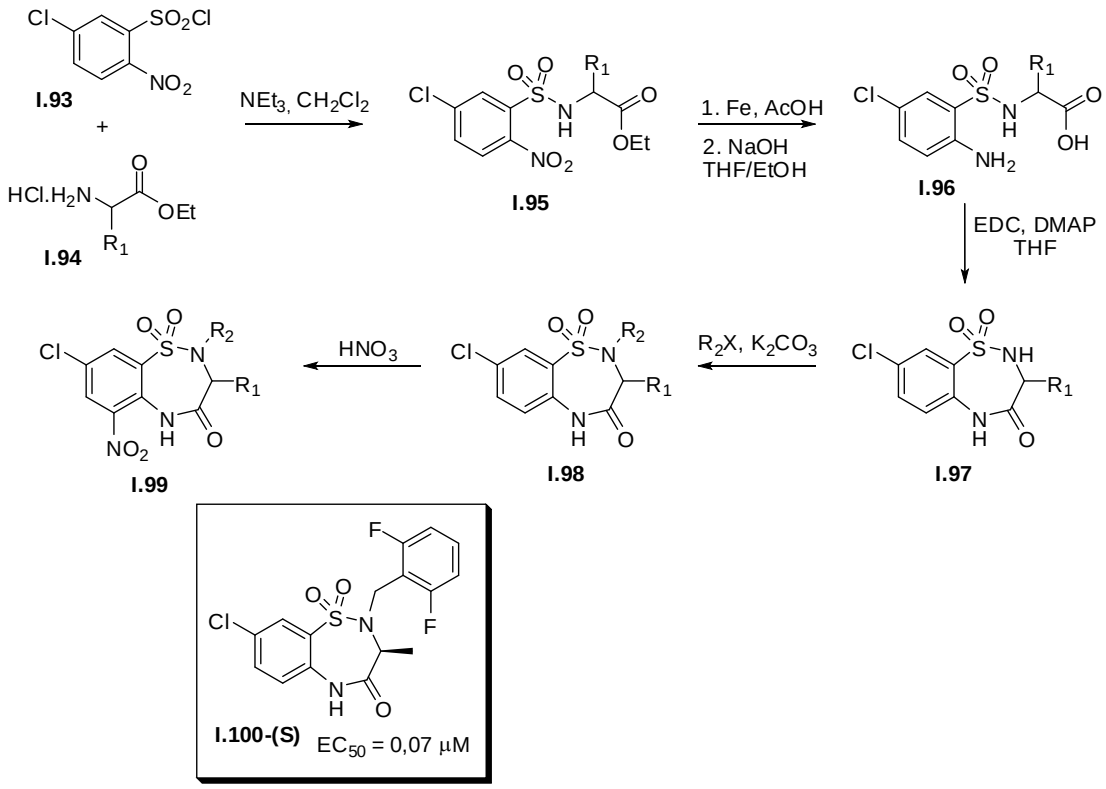


Figure I.27 *Synthesis of 2,3-dihydro-1,2,5-benzothiadiazepin-4-one-1,1-dioxides by Di Santo & Artico*

After performing a chromatographic resolution of the most potent molecule in the series, 8-chloro-2-(2,6-difluorobenzyl)-2,3-dihydro-3-methyl-1,2,5-benzothiadiazepin-4(5*H*)-one-1,1-dioxide **I.100**, an X-ray analysis of both enantiomers was performed. Interestingly, in the solid state the N2 atom seems to behave like a chiral centre in both enantiomers, displaying both the S and R configuration.

Other related structures that were synthesized consist of the 2,3-dihydro-3-hydroxy-1,2,5-benzothiadiazepine-1,1-dioxides **I.101** [144] and 1-[2-(4-methoxyphenyl)ethyl]-benzo[c]-1,2-dihydro-pyrido[2,3-f][1,2,5]thiadiazepine-5,5-dioxide **I.102**[145] (*figure **I.28***).

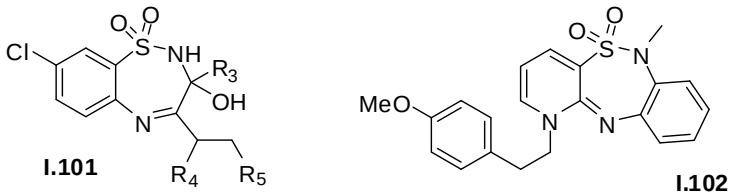


Figure I.28 *Other benzothiadiazepine analogs **I.101** and **I.102** found in literature*

[144] Loukou, C.; Patel, N.; Foucher, V.; Hemming, K. *J. Sulfur Chem.* **2005**, *26(6)*, 455-479.
[145] Gallet, S.; Flouquet, N.; Carato, P.; Pfeiffer, B.; Renard, P.; Léonce, S.; Pierré, A.; Bertholet, P.; Lebegue, N. *Bioorg. Med. Chem.* **2009**, *17(3)*, 1132-1138.

7.2. 1,2,5-THIADIAZEPAN-4-ONE-1,1-DIOXIDES

In contrast with the structural simplicity of this scaffold, it was only described in 1991 for the first time as an intermediate **I.103** for the synthesis of a tricyclic oxa-cyclol peptide **I.104**[146] (*figure **I.29-A***). Another thiadiazepane **I.108** was synthesized by Liskamp *et al.* in 1996 as a structural analog of classic diketopiperazines[147], but this was mainly a side project of his main goal namely the synthesis of β-peptidosulfonamides. To synthesize the thiadiazepane, Liskamp applied a solid phase strategy using an α-amino acid and a β-aminoethanesulfinyl chloride **I.106** as main building blocks (*figure **I.29-B***). First, a Fmoc-protected α-amino acid was coupled onto Tentagel resin, followed by deprotection and subsequent coupling of the Boc-protected (S)-2-benzyl-2-aminoethanesulfinyl chloride. Oxidation to the sulfonamide using OsO_4/NMMO and removal of the Boc group with TFA/CH_2Cl_2 then allowed the cyclization and concomitant cleavage of the thiadiazepane **I.108** by refluxing the resin for 5 days in the presence of triethylamine.

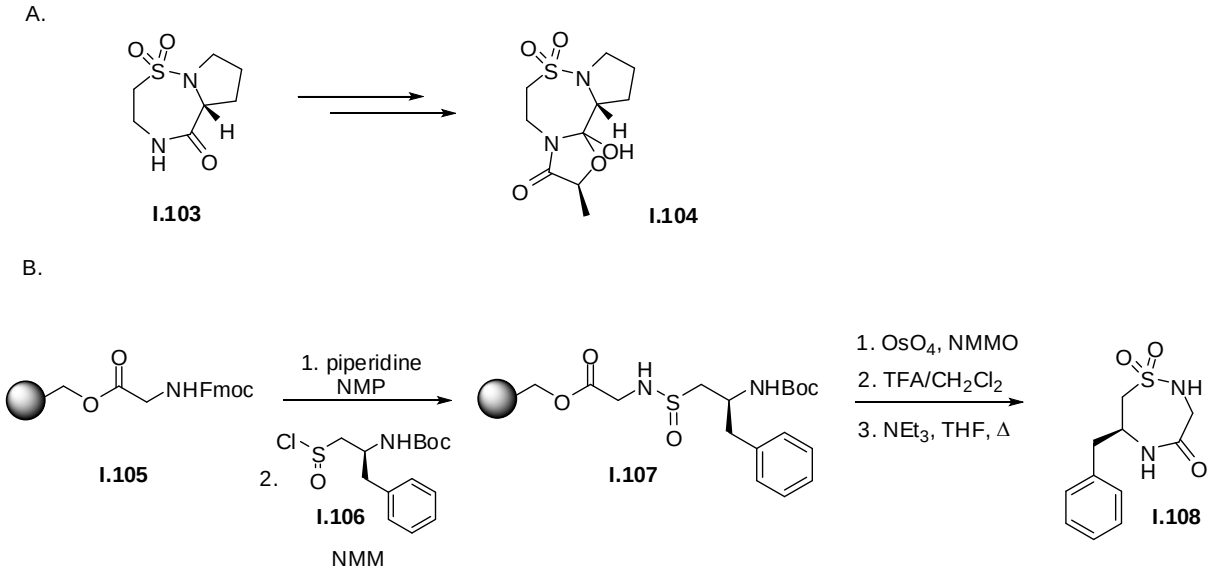


Figure I.29 A. *Thiadiazepanone **I.103** as intermediate for oxa-cyclol peptide **I.104 B.** Synthesis of a 1,2,5-thiadiazepan-4-one-1,1-dioxide **I.108** by Liskamp et al.*

In 2009 however, a DOS approach towards different sultams was reported by Hanson et al.[148], making use of tertiary vinyl sulfonamides carrying various functional groups. Depending on the functionalities that were present on this intermediate, different methodologies could be applied to form an array of sultams with different ring-shapes. Formation of the thiadiazepanes **I.111** started from the intermediate **I.110**, built up via 2-chloroethanesulfonyl chloride, the methyl ester of L-valine or L-phenylalanine, allyl bromide and a primary amine (*figure **I.30***). Hydrolysis of the methyl ester in the presence of lithium hydroxide followed by lactam formation using DCC afforded compounds **I.111**.

[146] Calcagni, A.; Gavuzzo, E.; Lucente, Gino; Mazza, Fernando; Pinnen, F.; Pochetti, G.; Rossi, D. *Int. J. Pept. Protein Res.* **1991**, *37(3)*, 167-173.
[147] de Bont, D. B. A.; Moree, W. J.; Liskamp, R. M. J. *Bioorg. Med. Chem.* **1996**, *4(5)*, 667-672.
[148] Zhou, A.; Rayabarapu, D.; Hanson, P. R. *Org. Lett.* **2009**, *11(3)*, 531-534.

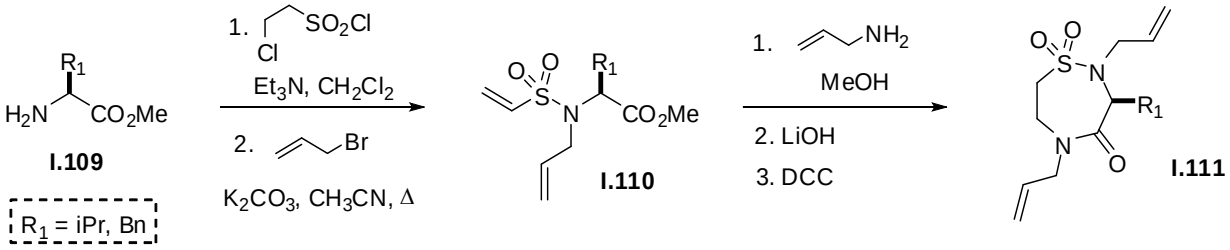


Figure I.30 *Synthesis of thiadiazepan-4-one-1,1-dioxides by Hanson et al.*

These 2 thiadiazepanes were the prelude for the automated synthesis of a library consisting of 184 members diversified at 3 positions[149] (*figure **I.31***). First, 3 basic thiadiazepanes **I.113** were synthesized as described above, all bearing a 4-bromobenzylgroup of the N_2 position and a propynyl substituent at the N_5 position.

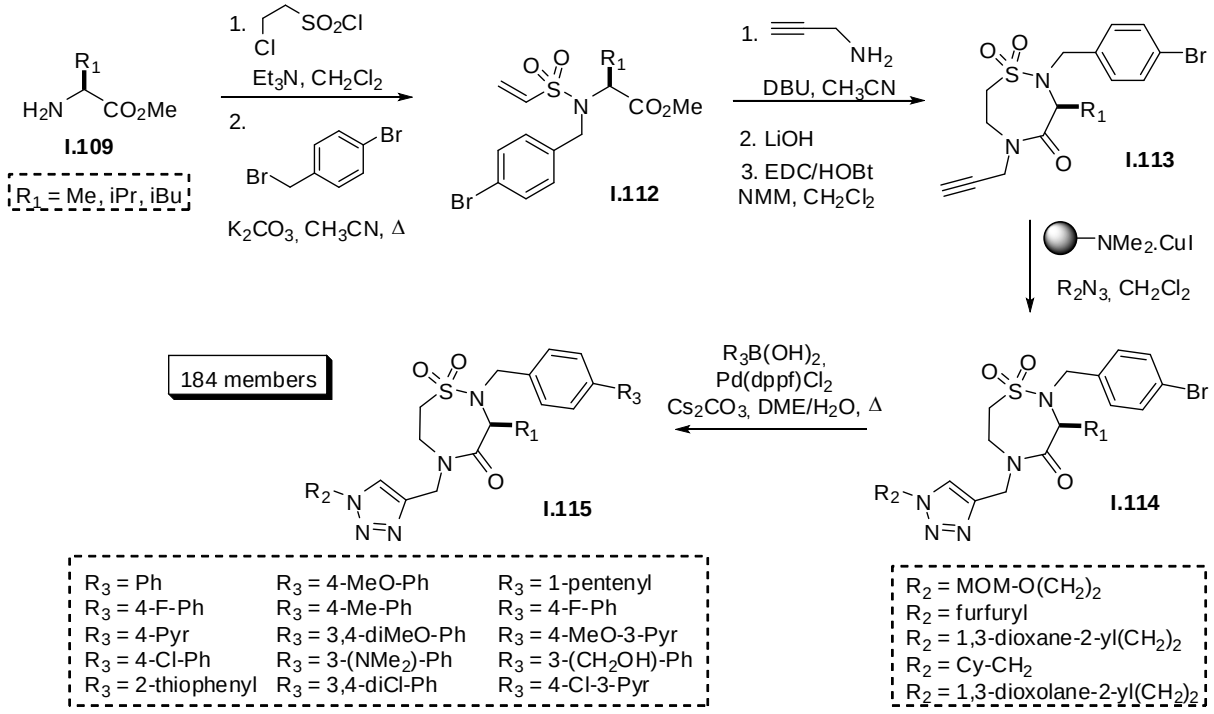


Figure I.31 *Synthesis of a 184 membered library of thiadiazepanes by Hanson et al.*

In a two-step procedure, performing a Huisgen [3+2] cycloaddition with 5 different alkyl azides and a Suzuki-Miyaura cross-coupling reaction using 15 boronic acids, a theoretical library of 225 members was formed. However, only 184 members could be isolated with a purity >90% and a satisfying yield.

7.3. 1,2,6-BENZOTHIADIAZOCIN-5-ONE-1,1-DIOXIDES

An almost unexplored class of molecules are the 8-membered structural analogs of the 2,3-dihydro-1,2,5-benzothiadiazepin-4(5*H*)one-1,1-dioxides **I.68**, namely the 3,4-dihydro-2*H*-1,2,6-

[149] Fenster, E.; Long, T. R.; Zang, Q.; Hill, D.; Neuenswander, B.; Lushington, G. H.; Zhou, A.; Santini, C.; Hanson, P. R. *ACS Combi. Sci.* **2011**, *13(3)*, 244-250.

benzothiadiazocin-5(6*H*)-one-1,1-dioxides **I.70**. To our knowledge, only related structures such as dibenzo[c,g][1,2,6]thiadiazocin-5-one-12,12-dioxides **I.116** [150] , pyrrolo[1,2-a][3,1,6]benzothiadiazocines **I.117** [151] , 9H-pyrrolo[2,1-b][1,3,6]-benzothiadiazocin-10(H*11*)-ones **I.118** [152] and 10*H*-pyrrolo[1,2-b][1,2,5]benzothiadiazocin-4-one-5,5-dioxide **I.119** [153] have been described in the literature (*figure **I.32***). These benzothiadiazocines **I.70** have probably been ignored due to the difficulties associated with the ring closure of 8-membered lactams[154]. However, the scaffold itself is interesting because it can be diversified at several positions and it has a good pharmacokinetic profile.

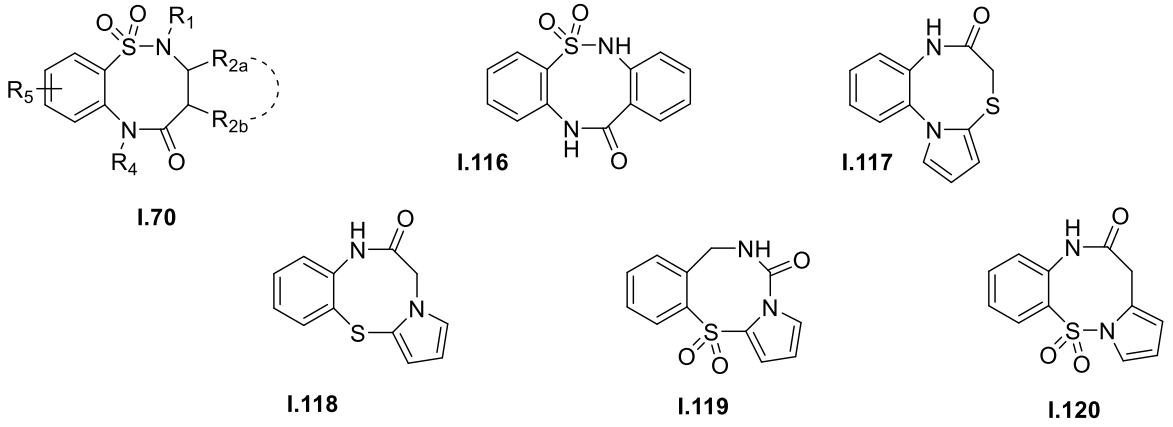


Figure I.32 *Benzothiadiazocines described in the literature*

[150] Nakanishi, M.; Oita, N.; Munakata, T.; Tsumagari, T. *US Patent* 3555012 **1971**.
[151] a) Cheeseman, G. W. H.; Hawi, A. A.; Varvounis, J. *J. Heterocycl. Chem.* **1985**, *22(2)*, 423-427. b) Cheeseman, G. W. H.; Varvounis, J. *J. Heterocycl. Chem.* **1987**, *24(4)*, 1157-1161.
[152] Silvestri, R.; Pagnozzi, E.; Artico, M.; Stefancich, G.; Massa, S.; La Colla, P. *J. Heterocycl. Chem.* **1995**, *32(2)*, 683-685.
[153] Di Santo, R.; Costi, R.; Artico, M.; Massa, S. *J. Heterocycl. Chem.* **1995**, *32(6)*, 1779-1782.
[154] Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14(4)*, 95-102.

7.4. CONCLUSION & PROJECT AIM

Although they had already proven to be valuable, the benzothiadiazepinones **I.68**, the thiadiazepanones **I.69** and the benzothiadiazocinones **I.70** remain underexplored classes of scaffolds in the search for biologically active compounds. Therefore, the aim of this project is to develop a new synthetic route towards these scaffolds, allowing a thorough exploration of their surrounding chemical space.

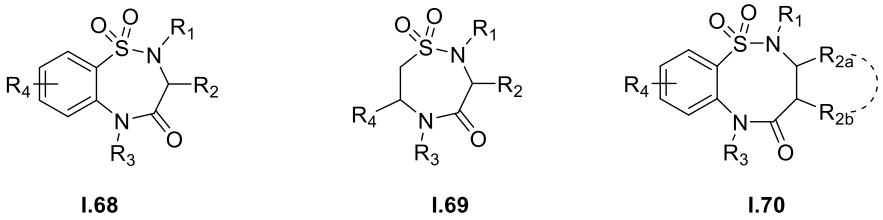


Figure I.33 *Target scaffolds*

To obtain this goal, it was considered that a parallel synthesis strategy performed on solid phase would be the most convenient method. This approach allows a fast introduction of structural diversity and leaves the possibility to automate the process, once a synthetic strategy is optimized. To increase the ease of integrating structural diversity in our scaffolds, the use of commercially available or readily accessible building blocks will be implemented as much as possible in the applied synthetic strategy. The structural resemblance between these three scaffolds types is also an advantage, as a similar synthetic pathway can be followed to build them up.

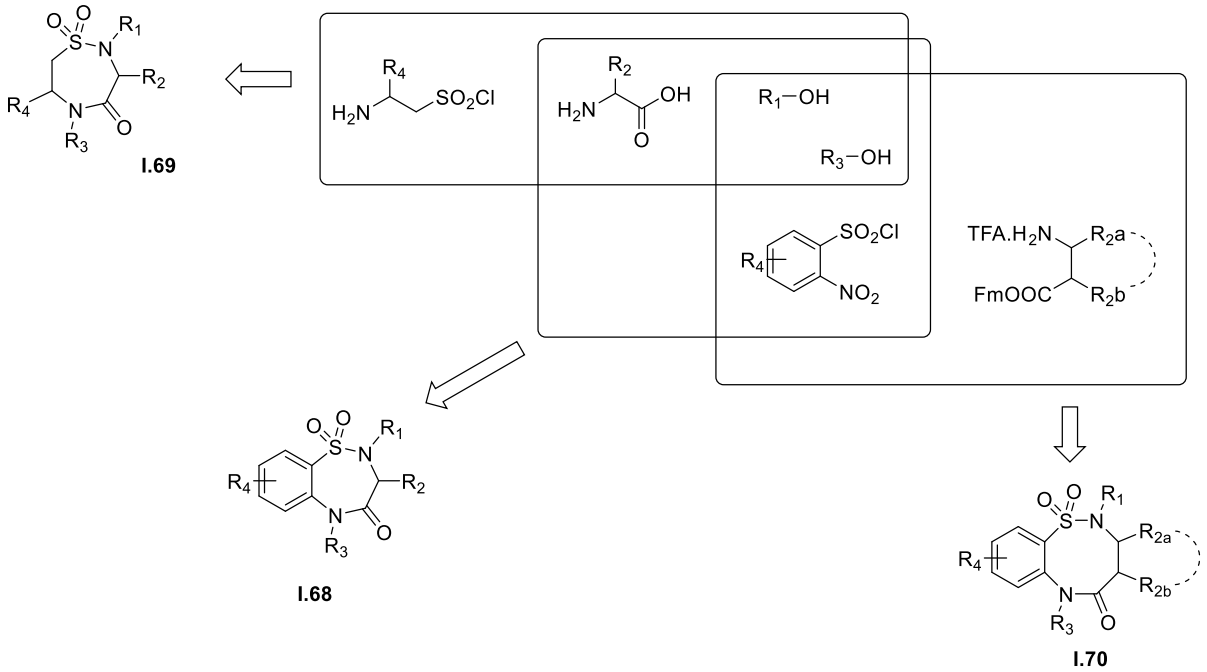


Figure I.34 *Target scaffolds and their building blocks*

After evaluation, the most suited strategy for each type of scaffold will be determined and applied for the synthesis of a small library.

CHAPTER II: SYNTHESIS

1 SYNTHESIS OF THE TARGET COMPOUNDS

To synthesize the target molecules, a similar strategy could be applied in all three cases because of their structural resemblance. Indeed, a retrosynthetic analysis of all target compounds reveals that the most obvious disconnections are the sulfonamide bond and the amide bond. The amide bond formation however was chosen as the final step of all the syntheses, because this allowed the use of two different synthetic methods to obtain the desired compounds (*figure **II.1***). The first method consisted of a so called *cyclization/release* strategy, which combines the ring closure with the cleavage of the desired product. The second method was an *on-resin cyclization*, which kept the ring closed product attached to the solid support after amide bond formation. Both methods have their intrinsic advantages and disadvantages (*vide infra*).

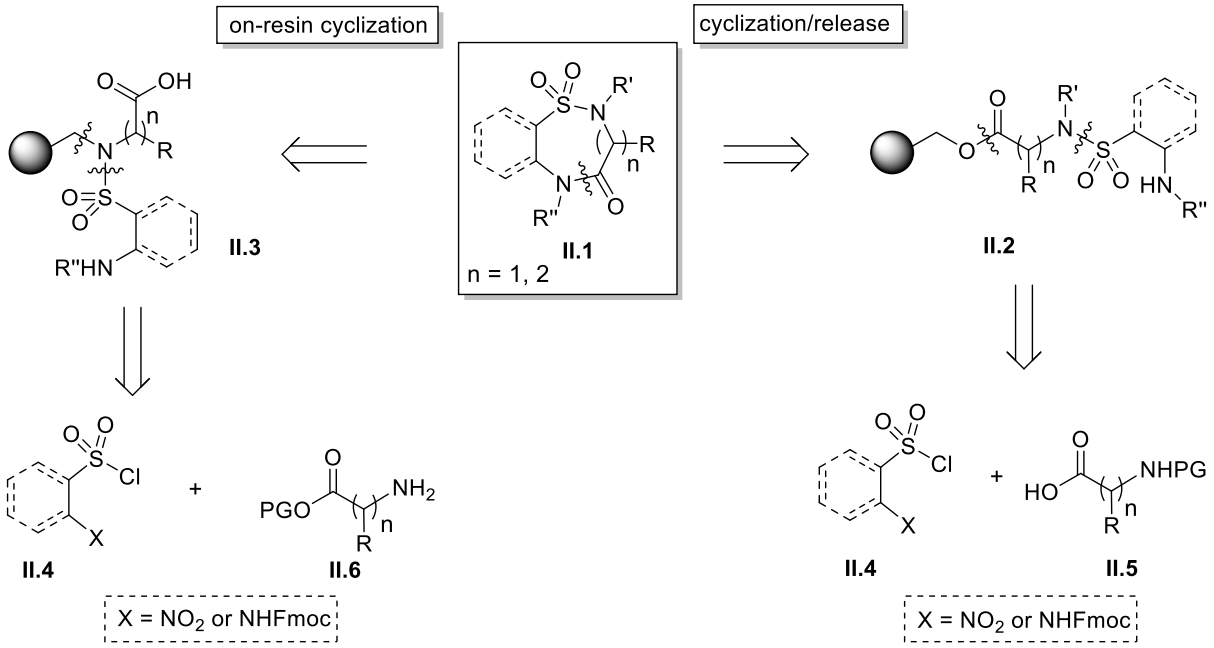


Figure II.1 *Retrosynthetic scheme using two different synthetic strategies: cyclization release and on-resin cyclization*

Breaking the amide bond delivers ring precursor **II.2**, in the case of the cyclization/release strategy, or ring precursor **II.3**, in the case of the on-resin cyclization. Both precursors can now be divided into a sulfonylchloride part and an amino acid part. The sulfonylchloride can either be a 2-nitrobenzenesulfonylchloride, if the benzoannelated scaffolds are desired, or a Fmoc-protected 2-aminoethanesulfonyl chloride, if the monocyclic thiadiazepanes are wanted. The use of an α-amino acid will deliver a seven membered compound, a β-amino acid an eight membered benzothiadiazocinone. The specific synthetic strategy for each target scaffold will be outlined in detail in the next sections.

1.1 CYCLIZATION/RELEASE VS. ON-RESIN CYCLIZATION

The cyclization/release strategy or cyclative cleavage is part of the so-called traceless linker methods, in which there is no functional group residue (*trace*) left after cleavage[155]. The cyclization/release strategy consists in most cases of reacting a nucleophilic functionality present on the acyclic precursor with an electrophilic functionality of the linker. This not only induces ring closure, but also the release of the ring-closed product from the solid support. An advantage of this strategy is that only ring-closed products will be cleaved from the resin, resulting in a product that is relatively pure. A disadvantage is that on-resin scaffold decoration needs to happen before ring closure. Most examples of this strategy make use of a nitrogen atom as the nucleophile and an ester or amide moiety as solid phase anchor functionality, resulting in the formation of five-[156], six-[157] or seven-membered lactams[158]. The success of this approach not only depends on the nucleophilicity and electrophilicity of both the reaction partners, but also on steric factors.

Using the on-resin cyclization strategy, the ring closed products remain anchored onto the solid support. The main advantages of this approach are the possibility to derivatize the cyclized product further on-resin and to activate both reaction partners involved during the ring closure. Main disadvantages are the loss of one diversity position (the anchoring point) and the usually decreased purity of the final products compared to the cyclization-release approach, because cleavage is not selective for the ring closed products. Both methods are illustrated in the case of the 2,3-dihydro-1,2,5-benzothiadiazepin-4(5*H*)-one-1,1-dioxides (*figure **II.2***).

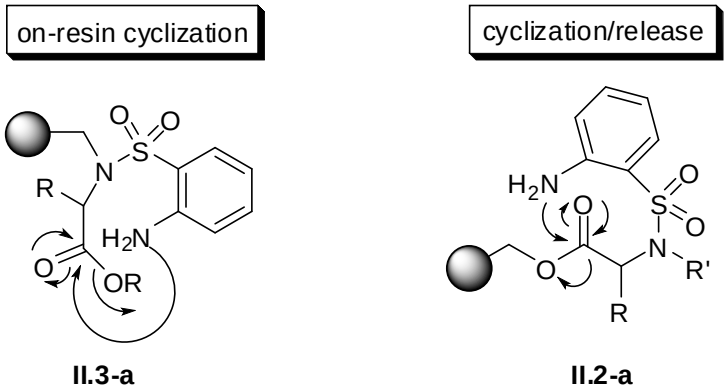


Figure II.2 *Mechanisms of the on-resin cyclization and cyclization/release strategy*

[155] Blaney, P.; Grigg, R.; Sridharan, V. *Chem. Rev.* **2002**, *102(7)*, 2607-2624.
[156] a) Wilson, L. J.; Li, M.; Portlock, D. E. *Tetrahedron Lett.* **1998**, *39(29)*, 5135-5138. b) Blass, B. E.; Srivastava, A.; Coburn, K. R.; Faulkner, A. L.; Janusz, J. J.; Ridgeway, J. M.; Seibel, W. L. *Tetrahedron Lett.* **2004**, *45(6)*, 1275-1277. c) Li, M.; Wilson, L. J. *Tetrahedron Lett.* **2001**, *42(8)*, 1455-1458.
[157] a) Pathak, R.; Roy, A. K.; Batra, K. S. *Tetrahedron Lett.* **2005**, *46(32)*, 5289-5292. b) Guo, T.; Adang, A. E. P.; Dong, G.; Fitzpatrick, D.; Geng, P.; Ho, K.-K.; Jibilian, C. H.; Kultgen, S. G.; Liu, R.; McDonald, E.; Saionz, K. W.; Valenzano, K. J.; van Straten, N. C. R.; Xie, D.; Webb, M. L. *Bioorg. Med. Chem. Lett.* **2004**, *14(7)*, 1717-1720. c) Mieczkowski, A.; Kozminski, W.; Jurczak, J. *Synthesis* **2010**, 221-232.
[158] a) Smith, R. A.; Bobko, M. A.; Lee, W. *Bioorg. Med. Chem. Lett.* **1998**, *8(17)*, 2369-2374. b) Mayer, J. P.; Zhang, J.; Bjergarde, K.; Lenz, D. M.; Gaudino, J. J. *Tetrahedron Lett.* **1996**, *37(45)*, 8081-8084.

2 2,3-DIHYDRO-1,2,5-BENZOTHIADIAZEPIN-4(5*H*)-ONE-1,1-DIOXIDES

2.1 SYNTHESIS VIA THE CYCLIZATION/RELEASE STRATEGY

2.1.1 RETROSYNTHETIC OVERVIEW

As been described in the general overview of the target compounds, the most logic disconnection in the benzothiadiazepinone **II.7** is the amide bond (*figure **II.3***). When opened, ring closing precursor **II.8** appears in which the sulfonamide bond can be disconnected, affording two general building blocks: the 2-nitrobenzenesulfonyl chlorides **II.9** and the N-Fmoc protected α-amino acids **II.13**. The α-amino acids are commercially available, the 2-nitrobenzenesulfonyl chlorides **II.9** can readily be synthesized from substituted 2-nitrophenols **II.11**. The success of this approach will probably depend on the final lactam formation. In the case this strategy wouldn't work, the alternative on-resin cyclization could still be applied (*vide infra*).

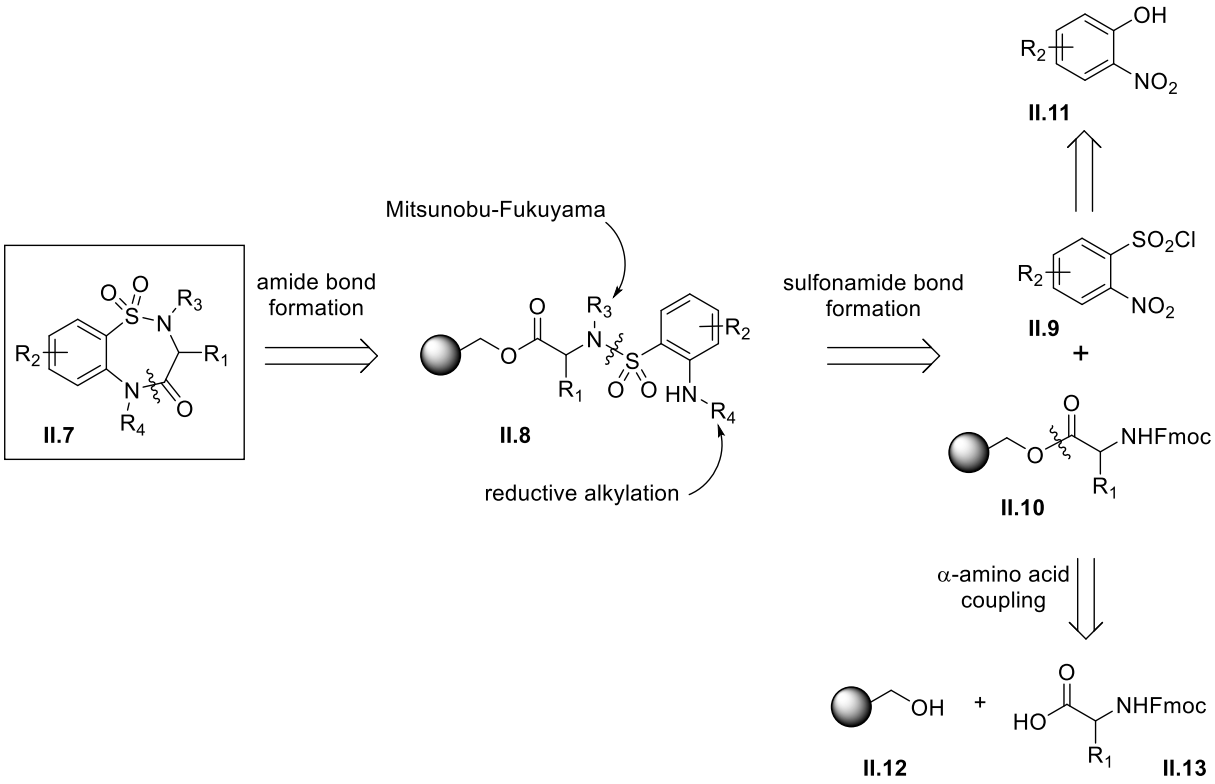


Figure II.3 *Retrosynthetic scheme towards the 2,3-dihydro-1,2,5-benzothiadiazepin-4(5H)-one-1,1-dioxides*

2.1.2 2-NITROBENZENESULFONYL CHLORIDES

To build the benzothiadiazepinones and benzothiadiazocinones, 2-nitrobenzenesulfonyl chlorides **II.9** are required. Although some substituted 2-nitrobenzenesulfonylchlorides are commercially available,

using only those would severely limit the possibilities to explore the chemical space around the benzene moiety. Therefore, a short synthesis towards these building blocks needed to be devised, starting from a common precursor with a broadly variable substitution pattern.

The main issue in most syntheses towards these building blocks is the introduction of the sulfur atom on the benzene moiety, which can be achieved in several ways. One example describes the nucleophilic aromatic substitution of chlorine using benzylmercaptane[159] (*figure **II.4-A***). The resulting mercaptane is then converted to the desired sulfonyl chloride **II.15** by an oxidative chlorination using chlorine gas in acetic acid. Another option is a Sandmeyer type reaction, in which an aniline **II.16** is converted to the corresponding diazonium salt and then immediately transformed into the sulfonyl chloride **II.17** using sulfurous acid in the presence of CuCl and $CuCl_2$[160] (*figure **II.4-B***). Both methods however, lack a broad substrate availability and compatibility.

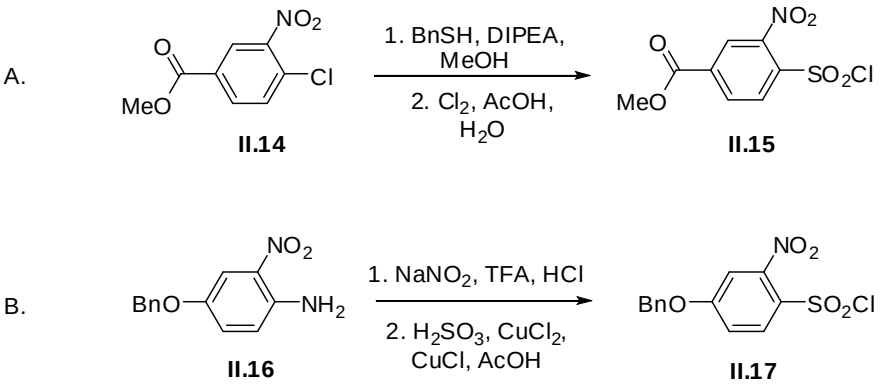


Figure II.4 *Two synthetic routes towards substituted 2-nitrobenzenesulfonyl chlorides* ***A.*** *via a SNAr reaction* ***B.*** *via a Sandmeyer type reaction*

A third method however, starting from 2-nitrophenols[161] **II.11** does not suffer these limitations and is therefore our method of choice (*figure **II.5-A***). The 2-nitrophenols were first converted to their corresponding O-thiocarbamates **II.18** using N,N-dimethylthiocarbamoyl chloride in the presence of potassium hydroxide. The O-thiocarbamoylation reaction of 4-formyl-2-nitrophenol **II.11-g** however readily delivered the dimethyl acetal. This product was transformed back to the desired O-(4-formyl-2-nitrophenyl) dimethylcarbamothioate **II.18-g** by stirring the acetal in a mixture of dioxane/water with a trace of hydrochloric acid.

A thermally induced Newman-Kwart rearrangement[162] then transformed the O-thiocarbamates to the S-thiocarbamates **II.19** in excellent yields. The elevated temperatures were needed for the formation of a 1,3-oxathietane transition state **II.22** from the O-thiocarbamates **II.18**, which subsequently collapses towards the thermodynamically more favored S-thiocarbamates **II.19** (figure **II.5-B**).

[159] Andrews, S. P.; Ladlow, M. *J. Org. Chem.* **2003**, *68(14)*, 5525-5533.
[160] Cherney, R. J.; Duan, J. J.-W.; Voss, M. E.; Chen, L.; Wang, L.; Meyer, D. T.; Wasserman, Z. R.; Hardman, K. D.; Liu, R.-Q.; Covington, M. B.; Qian, M.; Mandlekar, S.; Trzaskos, J. M.; Newton, R. C.; Magolda, R. L.; Wexler, R. R; Decicco, C. P. *J. Med. Chem.* **2003**, *46(10)*, 1811-1823.
[161] Percec, V.; Bera, T. K.; De, B. B.; Sanai, Y.; Smith, J.; Holerca, M. N.; Barboiu B.; Grubbs, R. B.; Fréchet, M. J. *J. Org. Chem.* **2001**, *66(6)*, 2104-2117.
[162] a) Kwart, H.; Evans, E. R. *J. Org. Chem.* **1966**, *31(2)*, 410-413 b) Newman, M. S.; Karnes, H. A. *J. Org. Chem.* **1966**, *31(12)*, 3980-3984.

Oxidative chlorination of the thiocarbamate using N-chlorosuccinimide in diluted hydrochloric acid finally delivered the desired building blocks **II.9-(a-h)** in good yields (table **II.1**). To avoid problems during chlorination with the free carboxylic acid of S-thiocarbamate **II.19-f**, an extra TMSE protecting step was implemented after performing the Newman-Kwart rearrangement .

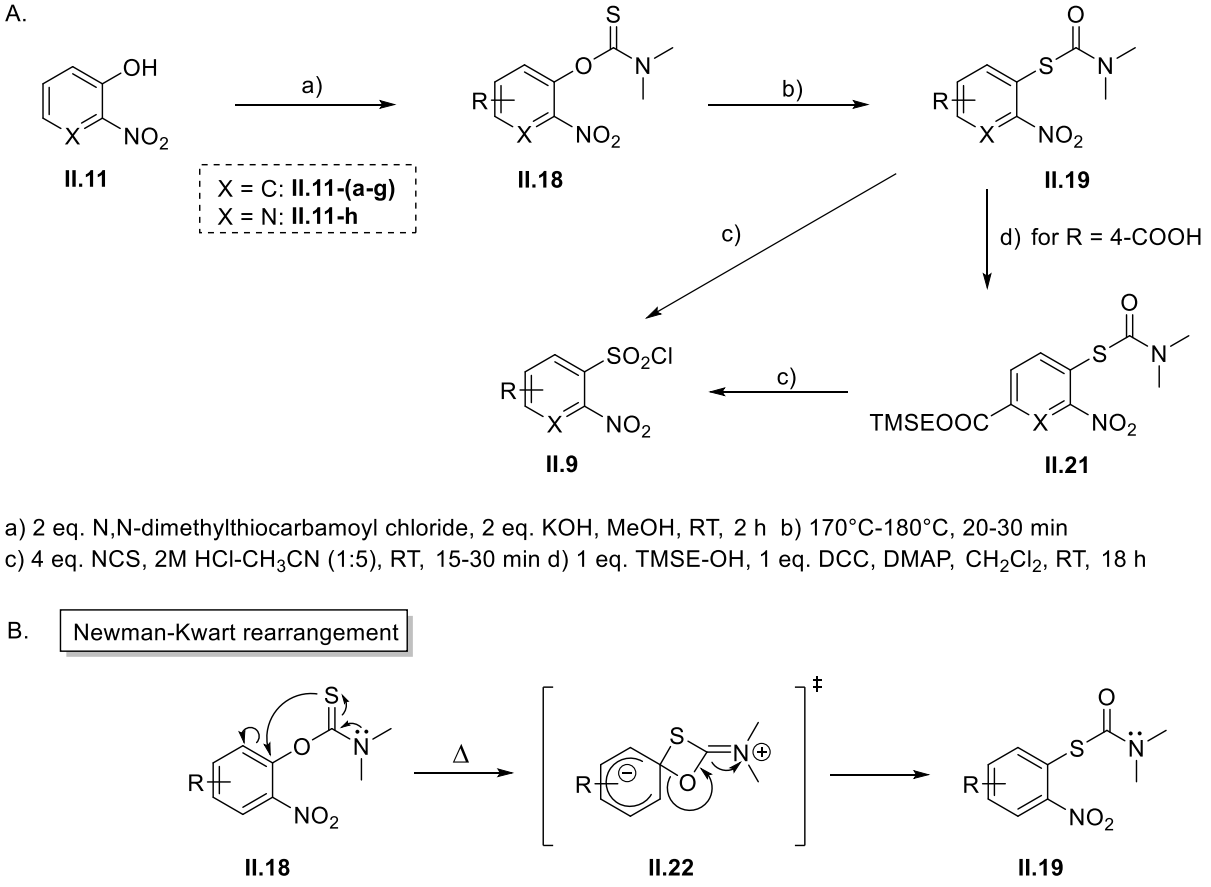


Figure II.5 A. *Synthesis of substituted 2-nitrobenzenesulfonyl chlorides* ***II.9*** *using a Newman-Kwart rearrangement* ***B.*** *Mechanism of the Newman-Kwart rearrangement*

PRODUCT	X	R	II.18	II.19	II.9	Overall
a	CH	4-Cl	92%	99%	84%	77%
b	CH	4-Br	97%	97%	83%	78%
c	CH	6-Br	56%	98%	85%	47%
d	CH	3-F	89%	95%	94%	79%
e	CH	5-F	94%	99%	71%	66%
f	CH	4-COOTMSE	29%	93%	38%[a]	10%
g	CH	4-CHO	83%[b]	95%	95%	75%
h	N	H	76%	92%	80%	56%

[a] yield over 2 steps: TMSE protection and oxidative chlorination

[b] yield over 2 steps: O-thiocarbamoylation and acetal deprotection

Table II.1 *Overview of the synthesized 2-nitrobenzenesulfonyl chlorides* ***II.9-(a-h)***

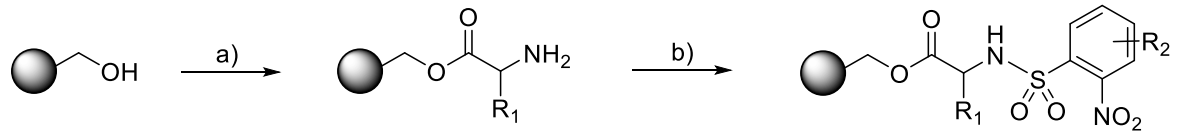
2.1.3 2,3-DIHYDRO-1,2,5-BENZOTHIADIAZEPIN-4(5*H*)-ONE-1,1-DIOXIDE SYNTHESIS

2.1.3.1 COUPLING OF THE α-AMINO ACIDS AND NOSYL BUILDING BLOCKS

For the optimization of the cyclization/release strategy, Wang resin **II.23** was chosen as solid support. This polystyrene based resin allows to cleave off the intermediates after each reaction step with TFA and thus to monitor the reactions with LC-MS. In a later stage, when reaction conditions are optimized for each step, the Wang resin can be replaced by another resin such as hydroxymethyl-polystyrene. The latter should allow a smoother cyclization/release reaction compared to the Wang resin, because the carbonylgroup of the ester linkage is more electrophilic[163].

Coupling of an N^{α}-Fmoc protected α-amino acid onto Wang resin was performed using classic conditions: preformation of the amino acid anhydride with DIC, followed by ester formation in the presence of DMAP (*figure **II.6***, step a). Fmoc deprotection with 4-methylpiperidine in DMF delivered **II.24** and allowed the attachment of 2-nitrobenzenesulfonyl chloride or building blocks **II.9-(a-h)** in the presence of *sym*-collidine (*figure **II.6***, step b).

The 2-nitrobenzenesulfonyl chloride has a triple function in this synthesis: it is used as a protective group, as an activating group and as a building block. Generally, 2-nitrobenzenesulfonyl chloride (or nosyl chloride) is used for protecting primary and secundary amines[164]. The nosyl group is stable under both strongly acidic and strongly basic conditions and hence orthogonal with several other protecting groups (strong reducing agents should be avoided)[165]. Removal of this protective group is induced by good nucleophiles such as a thiolates (e.g. β-mercaptoethanol in the presence of DBU). In our case however, the nosyl group also functions as a building block, with the 2-nitro group acting as a latent amine, so no deprotection is required. Nosyl protection is however especially useful for primary amines because of its activating properties, first described by Fukuyama[166]. After nosyl coupling, the resulting sulfonamide is acidic enough (pK_a 8-9) to allow a smooth alkylation using alkyl halides in mildly basic conditions or Mitsunobu conditions (*vide infra*), while the presence of the nosyl group prevents overalkylation.



II.23 **II.24** **II.25**

a) i. Fmoc-AA-OH, DIC, DMAP, CH_2Cl_2, RT, 16 + 3 h ii. 20% 4-methylpiperidine in DMF, RT, 2x10 min b) *o*-NsCl or **II.9**, *sym*-collidine, CH_2Cl_2, RT, 2x1 h

***Figure II.6** α-Amino acid coupling and 2-nitrobenzenesulfonyl chloride coupling*

[163] Park, K.-H.; Kurth, M. J. *Tetrahedron Lett.* **2000**, *41(39)*, 7409-7413.
[164] Kan, T.; Fukuyama, T. *Chem. Commun.* **2004**, *2004(4)*, 353-359.
[165] Greene, T. W.; Wuts; P. G. M. (2007) Protection for the Amino Group. In *Greene's Protective Groups in Organic Synthesis* (4th ed.) Hoboken, USA: Wiley-Interscience.
[166] a) Fukuyama, T.; Jow, C.-K.; Cheung, M. *Tetrahedron Lett.* **1995**, *36(36)*, 6373-6374. b) Fukuyama, T.; Cheung, M.; Jow, C.-K.; Hidai, Y.; Kan, T. *Tetrahedron Lett.* **1997**, *38(33)*, 5831-5834.

2.1.3.2 MITSUNOBU-FUKUYAMA ALKYLATION

2.1.3.2.1 THE MITSUNOBU-FUKUYAMA REACTION

The Mitsunobu reaction is one of the classic reactions in organic synthesis. Generally, it consists of the bimolecular nucleophilic substitution (SN2) of an alcohol **II.26** with a suitable nucleophile **II.27**, after activation as a leaving group in the presence of a phosphine and an azodicarboxylate[167] (*figure **II.7-A***). The classic nucleophile in this reaction is a carboxylic acid, yielding the corresponding (inverse) ester, but the scope is much broader than that. In fact, almost every relatively acidic compound type (pK_a <14) has been used as a suitable nucleophile in this reaction, such as phenols, thiols, imides, β-diketones, β-keto esters,... In this way Fukuyama introduced the 2- and 4-nitrobenzenesulfonamides **II.33**, possessing an acidic proton with an estimated pK_a of 8-9 as suitable nucleophiles in the Mitsunobu reaction[168]. This was an extremely useful reaction, because with sulfonyl chloride **II.32**, the nosyl group could easily be introduced on amine **II.31** but also readily removed again (*figure **II.7-B***). So now the nosyl group could be used as a temporary protecting and activating group for the selective mono-alkylation of an amine.

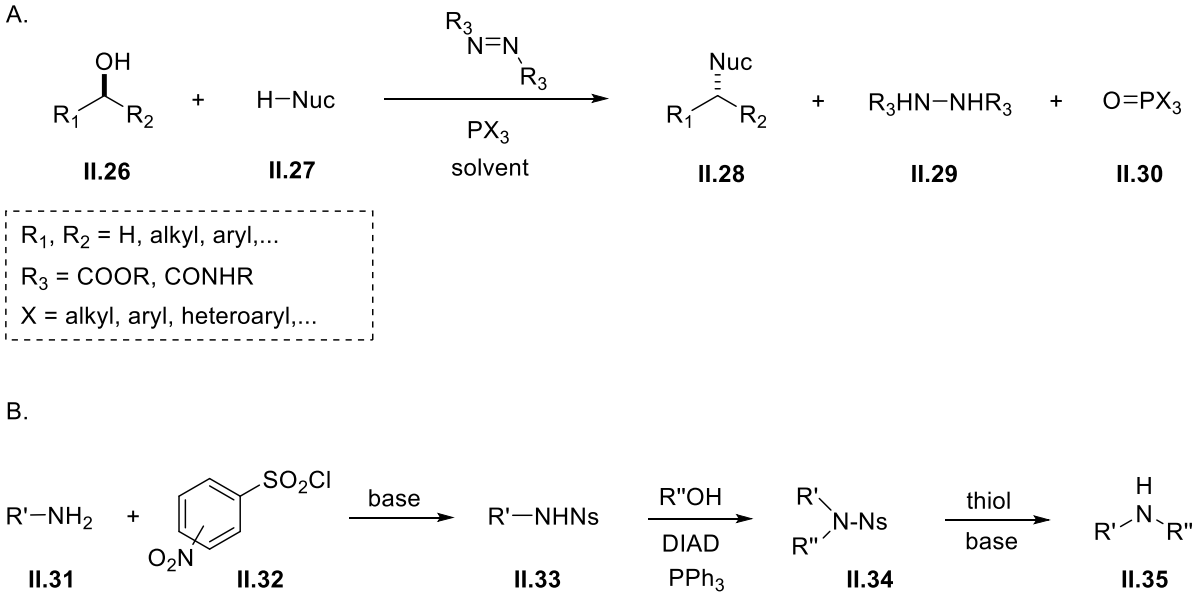


Figure II.7 A. *Classic Mitsunobu reaction* ***B.*** *Selective mono-alkylation of an amine using the Mitsunobu-Fukuyama protocol*

2.1.3.2.2 MITSUNOBU-FUKUYAMA ALKYLATION OF SULFONAMIDE **II.25**

After the introduction of our nosyl building block, Mitsunobu conditions were applied for the alkylation of the sulfonamide nitrogen of **II.25**, based on a similar procedure described in the literature[169]. Using 10 equivalents of an alcohol, 5 equivalents triphenylphosphine and diisopropyl azodicarboxylate

[167] Swamy, K. C. K.; Kumar, N. N. B.; Balaraman, E.; Kumar, K. V. P. P. *Chem. Rev.* **2009**, *109(6)*, 2551-2651.
[168] Fukuyama, T.; Yow, C.-K.; Cheung, M. *Tetrahedron Lett.* **1995**, *36(36)*, 6373-6374.
[169] Wels, B.; Kruijtzer, J. A. W.; Liskamp, R. M. J. *Org. Lett.* **2002**, *4(13)*, 2173-2176.

(DIAD), structurally varying alkyl chains could rapidly be introduced on the sulfonamide nitrogen, affording compounds **II.36** (*figure **II.8***).

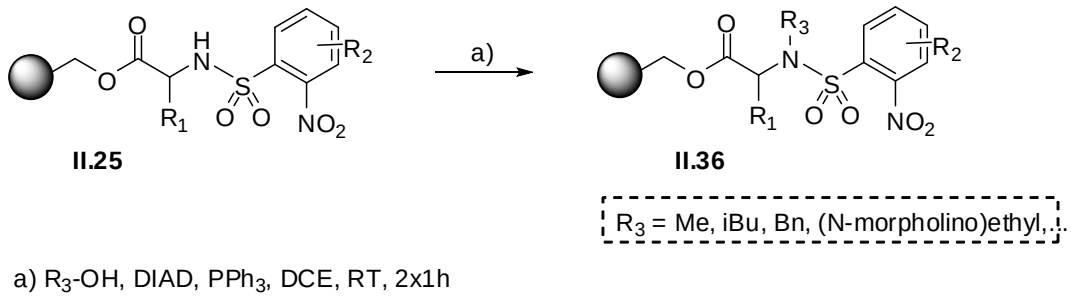


Figure II.8 *Mitsunobu-Fukuyama alkylation of sulfonamide **II.25***

2.1.3.3 REDUCTION OF THE NITRO GROUP

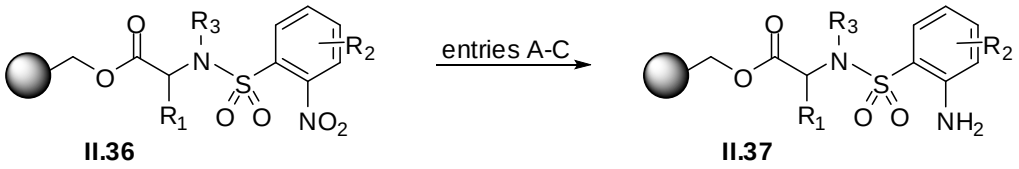


Figure II.9 *Nitro reduction of compound **II.36***

ENTRY	CONDITIONS
A	0,2 M $SnCl_2.2H_2O$, DMF, RT, 24 h
B	9 eq $Na_2S_2O_4$, 0,35 eq PTC-V^{2+}, 10 eq K_2CO_3, H_2O, THF, RT, 24 h
C	16 eq $CrCl_2$, DMF/MeOH 9/1, RT, 24 h
D	8 eq $CrCl_2$, DMF/MeOH 9/1, RT, 2x 1 h

Table II.2 *Test conditions for the nitro reduction of compound **II.36***

Reducing the nitro moiety should now readily deliver ring closing precursor **II.37** (*figure **II.9***). Generally, for the reduction of a nitro group on solid phase, tin(II) chloride is used as a reducing agent[170] (*table **II.2**,* entry A). In our case however, a test reaction using tin(II) chloride dihydrate in DMF resulted in a complex mixture of compounds (*figure **II.10***).

[170] a) Mayers, H. V.; Dilley, J.; Durgin, T. L.; Pavers, T. S.; Winssinger, N. A.; Zhu, H.; Pavia, M. R. *Mol. Diversity* **1995**, *1(1)*, 13-20. b) Lee, J.; Murray, W. V.; Rivero, R. A. *J. Org. Chem.* **1997**, *62(12)*, 3874-3879. c) Wei, G. P.; Phillips, G. B. *Tetrahedron Lett.* **1998**, *39(3)*, 179-182. d) Schwarz, M. K.; Tumelty, D.; Gallop, M. A. *J. Org. Chem.* **1999**, *64(7)*, 2219-2231.

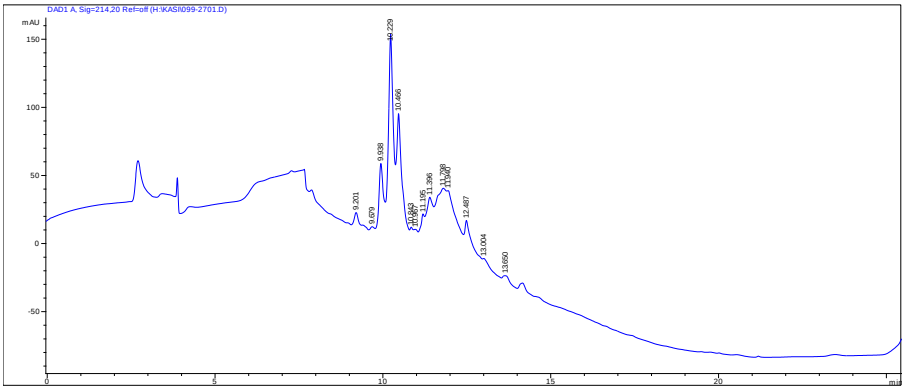


Figure II.10 *LC-chromatogram of the nitro reduction using $SnCl_2.2H_2O$* [171]

Two other methods were therefore tested, one making use of dithionite as a reducing agent[172], the other one making use of chromium(II) chloride[173]. The dithionite reduction was performed in the presence of the electron transfer catalyst ethyl viologen dibromide and potassium carbonate in a mixture of THF and water (*table* ***II.2****,* entry B). The viologen species is needed to mediate the reduction, while the dithionite is responsible for the recovery of the oxidized viologen species, as depicted in *figure* ***II.11***.

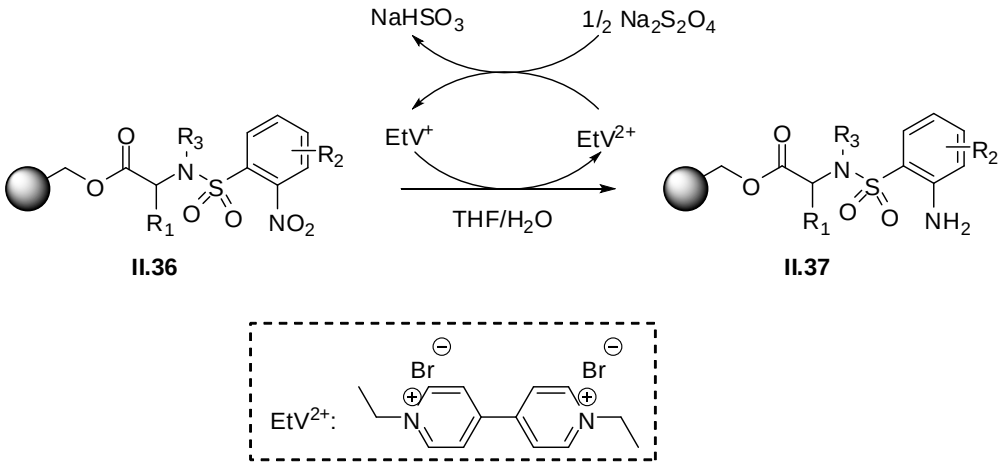


Figure II.11 *Dithionite reduction of the solid-bound* ***II.36*** *in the presence of ethyl viologen dibromide*

After 24 h, all the starting material was converted, but next to the desired aniline there were also some impurities visible in the LC-chromatogram (*figure* ***II.12***, LC-MS purity: 67%).

[171] column: Phenomenex Luna C18, gradient: CH_3CN/5mM NH_4OAc in H_2O in 22min.
[172] a) Park, K. K.; Oh, C. H.; Joung, W. K. *Tetrahedron Lett.* **1993**, *34(46)*, 7445-7446. b) Park, K. K.; Oh, C. H.; Sim, W.-J. *J. Org. Chem.* **1995**, *60(19)*, 6202-6204.
[173] Hari, A.; Miller, B. L. *Tetrahedron Lett.* **1999**, *40(2)*, 245-248.

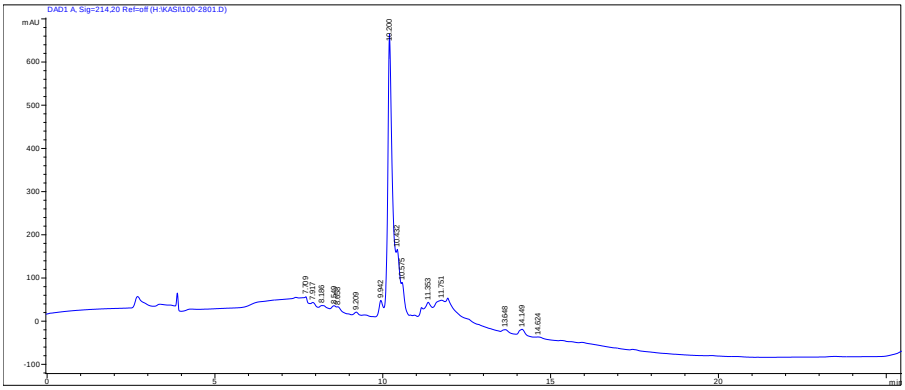


Figure II.12 *LC-chromatogram of the nitro reduction using $Na_2S_2O_4$* [171]

When using chromium(II) chloride in a mixture of DMF and methanol, a clean conversion to the aniline was achieved (*figure **II.13***, purity: 84%, entry C). The original reaction time and chromium(II) chloride amount, overnight stirring using 16 equivalents, were eventually reduced to twice 1 h stirring with 8 equivalents of chromium chloride with no negative effects on the conversion (*table **II.2**,* entry D). Another modification was the addition of methanol to the reaction mixture instead of using pure DMF. This protic solvent was an absolute requirement for the fast conversion towards the aniline.

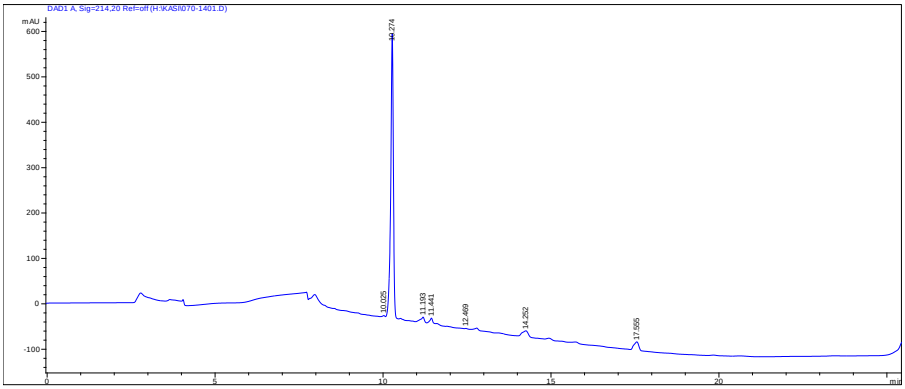


Figure II.13 *LC-chromatogram of the nitro reduction using $CrCl_2$*[171]

Other reducing conditions from the literature such as dithionite in refluxing ethanol[174], $NaBH_4$-$Cu(acac)_2$[175], In/NH_4Cl[176] or $Al/NiCl_2.6H_2O$[177] were not tested during this research.

2.1.3.4 N_5-ALKYLATION

Now that the nitro moiety was reduced, a fourth point of diversity could be introduced on the newly formed aniline **II.37**. First, the use of an alkyl halide in the presence of a base was considered, but overalkylation towards compounds **II.40** or **II.41** could occur when applying these conditions (*figure **II.14-A***). Another, indirect method consists of the formation of the amide **II.42**, followed by carbonyl reduction to the corresponding amine **II.39**[178]. This two-step synthesis however, is not the most

[174] Hughes, I. *Tetrahedron Lett.* **1996**, *37(42)*, 7595-7598.
[175] Phillips, G. B.; Wei, G. P. *Tetrahedron Lett.* **1996**, *37(28)*, 4887-4890.
[176] Kamal, A.; Reddy, G. S. K.; Reddy, K. L. *Tetrahedron Lett.* **2001**, *42(39)*, 6969-6971.
[177] Kamal, A.; Reddy, K. L.; .; Reddy, G. S. K. *Tetrahedron Lett.* **2003**, *44(25)*, 4741-4745.
[178] a) Manku, S.; Laplante, C.; Kopac, D.; Chan, T.; Hall, D. G. *J. Org. Chem.* **2001**, *66(3)*, 874-885. b) Pelletier, G.; Bechara, W. S.; Charette, A. B. *J. Am. Chem. Soc.* **2010**, *132(37)*, 12817-12819.

efficient procedure and is usually not compatible with a wide range of functionalities because of the strongly reducing agents needed for amide reduction (*figure **II.14-B***). A more suitable option seemed to be the direct reductive alkylation, which works under mildly acidic conditions (*figure **II.14-C***).

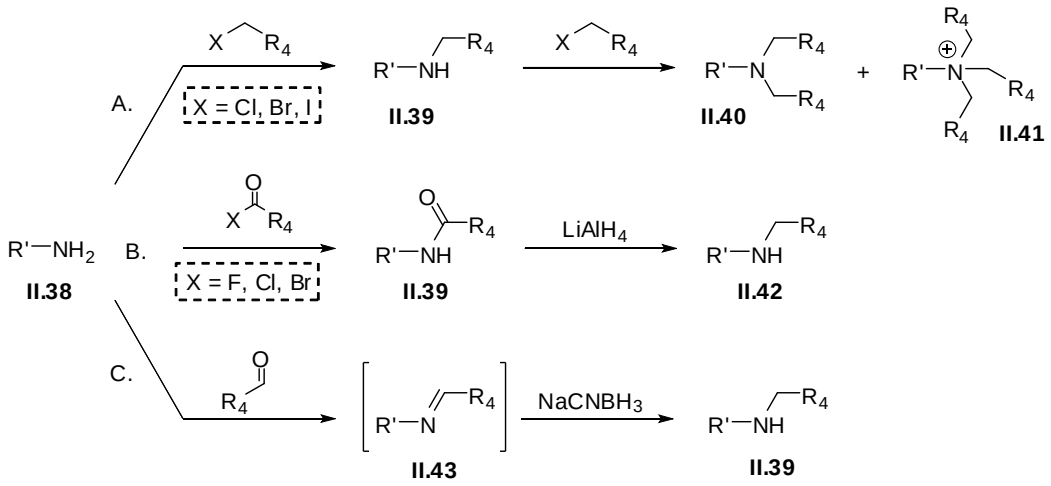
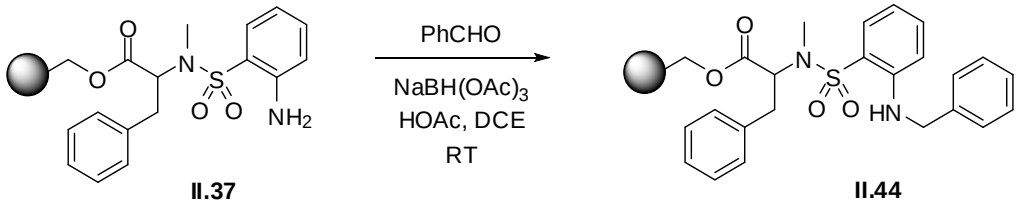


***Figure II.14** Methods for the alkylation at the N_5-position*

A commonly used reducing agent for this reaction is sodium cyanoborohydride[179], because of its stability in relatively acidic conditions and its solubility in polar solvents such as methanol. However, its hygroscopic nature combined with its toxicity makes this reagent not the most practical one to work with. An alternative reagent described by Abdel-Magid *et al.*[180] is sodium triacetoxyborohydride, which does not display these unpleasant properties. Also, this reagent proved to be superior in numerous cases compared to sodium cyanoborohydride, affording higher yields and higher purities.

As a model, we wanted to test the reductive alkylation of compound **II.37-b** towards the benzylated compound **II.44**. The test conditions for the reductive alkylation were based on the literature conditions described for aromatic amines substituted with an electron withdrawing substituent. It seemed that longer reaction times were necessary and more equivalents of each reagent had to be added to drive the reaction to completion. This is a consequence of the electron-poor aniline nitrogen, which slows down the imine formation during the reductive amination. These statements were proven by the results from our test cases (*table **II.3***). A slow progression was observed until a certain point was reached. Increasing the amount of reagents could however push the reaction towards the alkylated product. After stirring the resin for 55 h in the presence of 10 equivalents benzaldehyde, 6 equivalents $NaBH(OAc)_3$ and 10 equivalents of AcOH (entry G), a conversion of 1/99 was reached.



[179] Lane, C. F. *Synthesis* **1975**, *1975(3)*, 135-146.
[180] Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. S. *J. Org. Chem.* **1996**, *61(11)*, 3849-3862.

ENTRY	PhCHO [eq]	$NaBH(OAc)_3$ [eq]	AcOH [%]	TIME [h]	II.37-a/II.44-a [%]
A	6	3	2	8	42/58
B	6	3	2	24	27/73
C	6	3	2	72	40/60
D	6	4	4	8	30/70
E	6	4	4	24	28/72
F	10	6	10	8	44/56
G	10	6	10	55	1/99

Table II.3 *Test reactions for the reductive amination of the N_5-position using $NaBH(OAc)_3$*

After optimization of the conditions for benzaldehyde, aliphatic aldehydes such as acetaldehyde and valeraldehyde were tested under the same conditions and also delivered the desired alkylated products **II.44**. Overalkylation was not detected in the case of benzaldehyde or valeraldehyde and only in trace amounts when using acetaldehyde (<2%). The ring closure of these compounds is discussed separately from the non N_5-alkylated products, because the ring closing strategy needed to be adapted for the former type of structures (*vide infra*).

2.1.3.5 RING CLOSURE IN BASIC CONDITIONS

After reducing the nitro moiety of the nosyl group, the ring closure could be performed. The formation of 7-membered lactams however, is still considered as a challenging reaction in organic chemistry[181]. Next to the classic amide bond formation, many strategies have been developed in solution phase to obtain these medium-sized rings of which a few are depicted in *figure **II.15***.

The first example describes the intramolecular trapping of a ketene **II.46** that has been formed via a [1,5]H shift by heating the ethyl alkynyl ether **II.45**. The second example consists of a classic Beckmann rearrangement, in which a tosylated oxime **II.49** is treated with a Lewis acid, inducing the ring expansion towards the seven membered lactam **II.50**. A related reaction is the Schmidt reaction, in which a cyclohexanone **II.51** derivative is reacted with an azide, delivering lactam **II.53** after the loss of nitrogen. A last example describes the intramolecular Staudinger ligation[182] in which a peptide compound **II.54**, containing an azide and a free carboxylic acid moiety, is treated with the borane adduct of diphenylphosphanylmethanethiole **II.55** to deliver phosphanyl thioester **II.56**. Decomplexation of the phosphane with DABCO then triggers the Staudinger reaction, leading to lactam **II.57**.

[181] Nubbemeyer, U. *Top. Curr. Chem.* **2001**, *216*, 125-196.
[182] David, O.; Meester, W. J. N.; Bieräugel, H.; Schoemaker, H. E.; Hiemstra, H.; van Maarseveen, J. H. *Angew. Chem. Int. Ed.* **2003**, *42(36)*, 4373-4375.

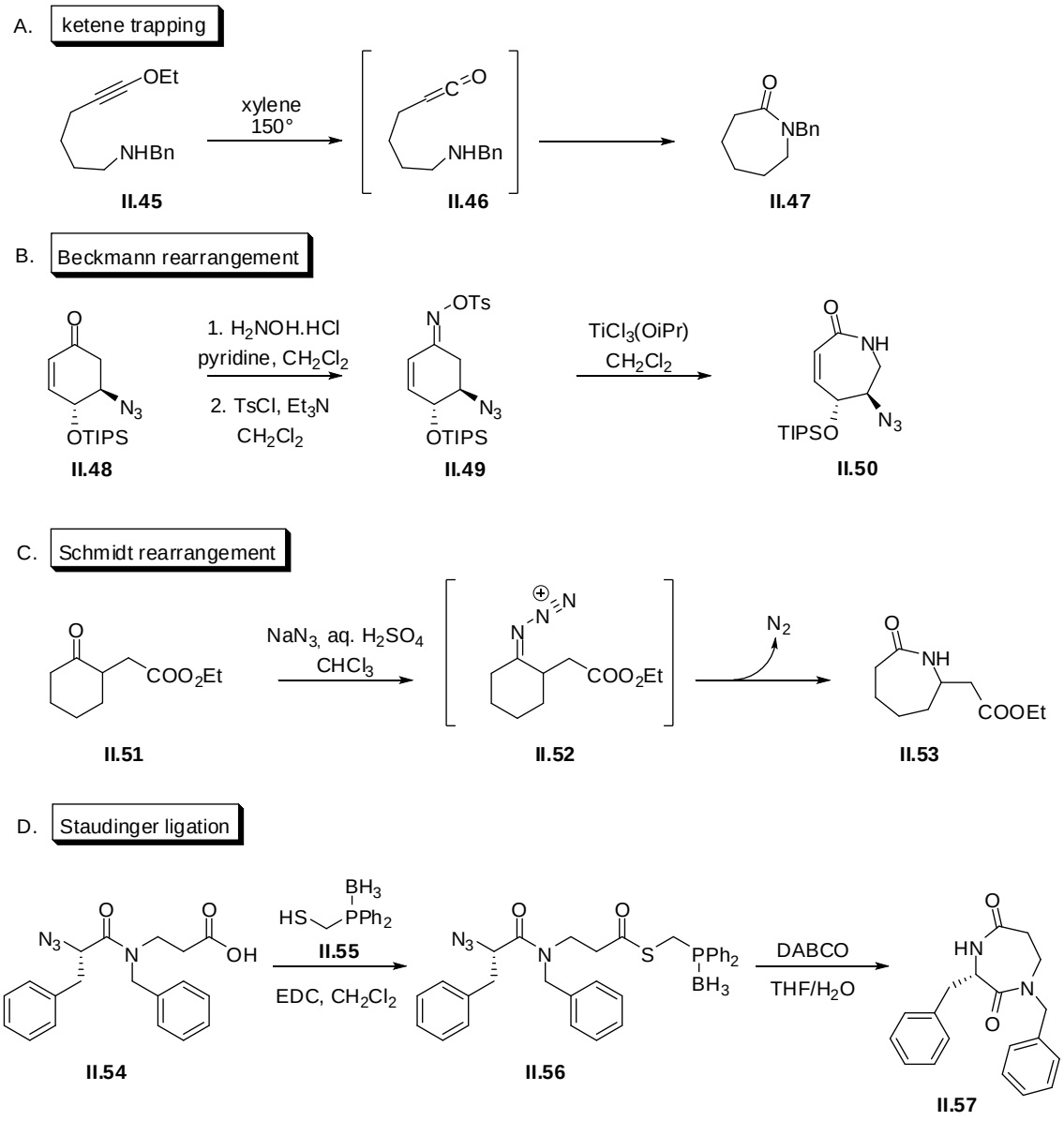


Figure II.15 *Some examples of 7-membered lactam syntheses*

Recent literature examples demonstrated however, that for the solid phase synthesis of 1,3-dihydro-1,4-benzodiazepin-2-ones **II.59** and 1,4-benzodiazepine-2,5-diones **II.61** different strategies could be applied. In the first case, ring closing precursor **II.58** was built up on Wang resin and ring closed by a cyclization/release protocol in an equal mixture of acetic acid and dichloroethane[183] (*figure **II.16-A***). In the latter case, 1,4-benzodiazepine-2,5-diones were produced by a cyclization/release reaction on Wang resin induced by heating precursor **II.60** in a 1M solution of sodium *tert*-butoxide in THF[184] (*figure **II.16-B***). An alternative strategy for the cyclization/release of these compounds was based on the use of Kaiser oxime resin as a solid support, which allowed the cyclative cleavage reaction of compound **II.62** in a mixture of AcOH and DIPEA[185] (*figure **II.16-B***).

[183] Laustsen, L. S.; Sams, K. *J. Comb. Chem.* **2007**, *9(6)*, 1094-1103.
[184] Mayer, J. P.; Zhang, J.; Bjergarde, K.; Lenz, D. M.; Gaudino, J. J. *Tetrahedron Lett.* **1996**, *37(45)*, 8081-8084.
[185] Smith, R. A.; Bobko, M. A.; Lee, W. *Bioorg. Med. Chem. Lett.* **1998**, *8(17)*, 2369-2374.

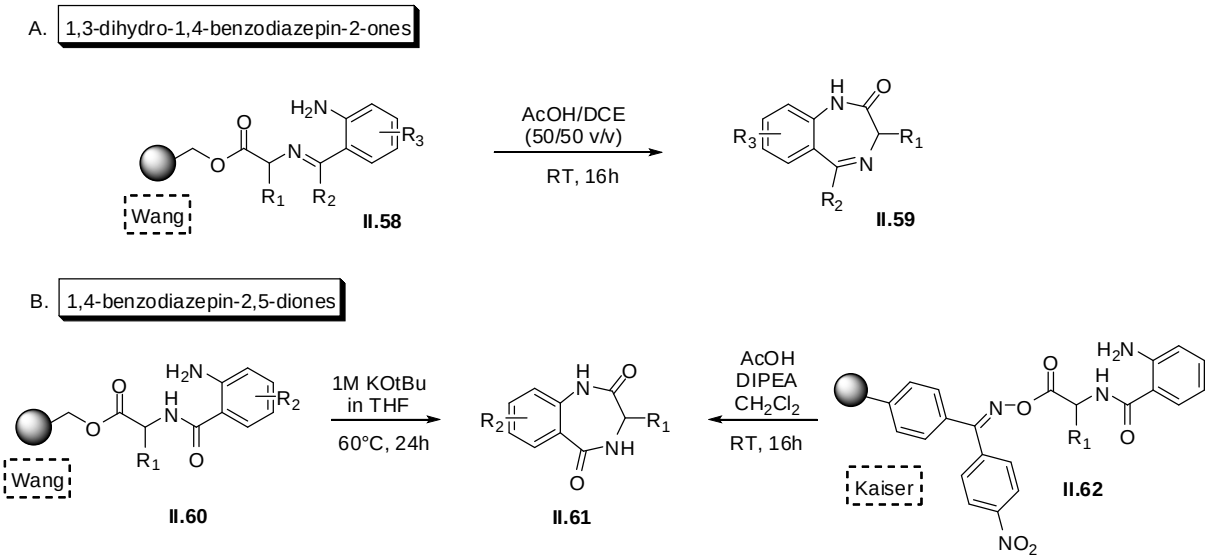
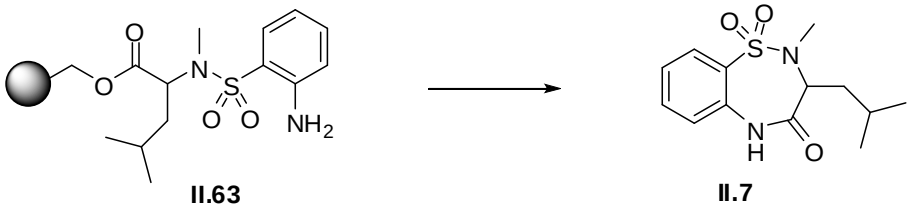


Figure II.16 A. *Synthesis of 1,3-dihydro-1,4-benzodiazepin-2-ones using mild acidic conditions* ***B.*** *1,4-benzodiazepin-2,5-diones using basic conditions or a buffered mixture of a mild acid and mild base.*

The ring closure in our case was tested for substrate **II.63**, built up from Fmoc protected leucine, nosyl chloride and methanol. The conditions were based on the literature procedures mentioned earlier and are presented in *table* ***II.4***. The first three entries consisted of tests with lithium *tert*-butoxide in different concentrations and at different temperatures. Entry A and B both delivered the desired product **II.7**, but in the case of entry A some ring closing precursor **II.63** was still present on the resin. In the case of entry C, there was no more ring closing precursor left on the solid support and product **II.7** was detected, but with a lot of indefinable impurities visible in the the LC-MS chromatogram. The conditions described in entry D and E couldn't deliver ring closed product, but in these cases there was still a lot of ring closing precursor left on the resin. Seemingly, these conditions were not potent enough to induce ring closure.



ENTRY	CONDITIONS	RESULT	RESIN RESIDUE
A	0,1 M LiO*t*Bu in THF, RT, 4 h	**II.7**	cleaved carboxylic acid
B	1 M LiO*t*Bu in THF, RT, 4 h	**II.7**	none
C	1 M LiO*t*Bu in THF, 60° C, 4 h	**II.7** + impurities	none
D	5 eq DIPEA, 2,2 eq AcOH, CH_2Cl_2, RT, 4 h	no product	cleaved carboxylic acid
E	10% DIPEA in THF, 60° C, 4 h	no product	cleaved carboxylic acid

Table II.4 *Results of the test reactions for the cyclization/release reaction using basic conditions*

The conditions from entry B were therefore chosen as the preferred ring closing conditions for the synthesis of a small library. The LC-MS chromatogram of the crude product is depicted in *figure* ***II.17***.

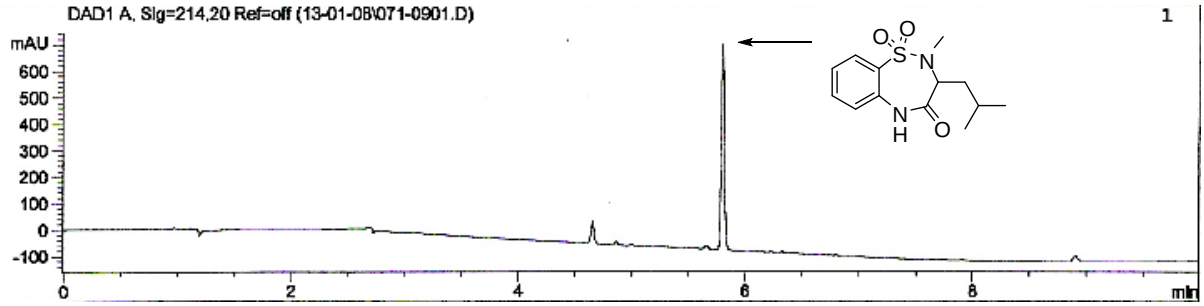
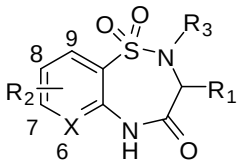


Figure II.17 *LC-MS chromatogram of the crude product after the cyclization/release reaction[186] (purity: 82%)*

Using these conditions, a small library of 27 molecules was built, diversified at three different positions by introducing different α-amino acids, nosyl building blocks and alcohols. The resulting compounds are listed in *table* ***II.5-A*** and *table* ***II.5-B***.



II.7

PRODUCT	R_1	R_3	YIELD (%)
a	H	H	39
b	iPr	H	16
c	Bn	Me	38
d	Bn	CH_2Bn	54
e	Bn	iBu	41
f	Bn	$C_{10}H_{21}$	35
g	Bn	2-(N-morpholino)ethyl	33
h	H	Bn	26
i	$(CH_2)_4NHBoc$	Me	54
j	4-(N-Trityl-imidazolyl)methyl	Me	38
k	3-(N-Boc-indolyl)methyl	Me	57
l	3-indolylmethyl	Me	44
m	3-(N-Boc-indolyl)methyl	Bn	62
n	Me	Me	58

[a] Yields are measured after purification and based upon the initial resin loading

Table II.5-A *Library of 2,3-dihydro-1,2,5-benzothiadiazepin-4(5H)-one-1,1-dioxides diversified at 2 positions (R_2 = H; X = CH)*

[186] column: Phenomenex Luna C18, gradient: CH_3CN/5mM NH_4Oac in H_20 in 22min.

PRODUCT	R_1	R_3	X	R_2 6	7	8	9	YIELD[a] (%)
o	iBu	Me	C	H	Cl	H	H	40
p	Bn	Me	C	H	Cl	H	H	23
q	H	Me	C	H	Cl	H	H	48
r	Bn	Me	C	H	Br	H	H	11
s	Bn	Me	C	H	H	F	H	24
t	H	Me	C	H	Br	H	H	56
u	H	Me	C	H	H	F	H	61
v	iBu	Bn	C	H	H	F	H	46
w	H	H	N	H	H	H	H	10
x	Bn	Me	N	H	H	H	H	5
y	iBu	Bn	N	H	H	H	H	18
z	Bn	Me	C	F	H	H	H	19
aa	4-(O*t*Bu)Bn	iBu	C	H	Br	H	H	23

[a] Yields are measured after purification and based upon the initial resin loading

Table II.5-B *Library of 2,3-dihydro-1,2,5-benzothiadiazepin-4(5H)-one-1,1-dioxides diversified at 3 positions*

The compound derived from Fmoc-Ser(tBu)-OH as building block however, could not be produced in this way. The basic ring closing conditions appeared to induce an elimination reaction, leading to product **II.66** (*figure **II.18***).

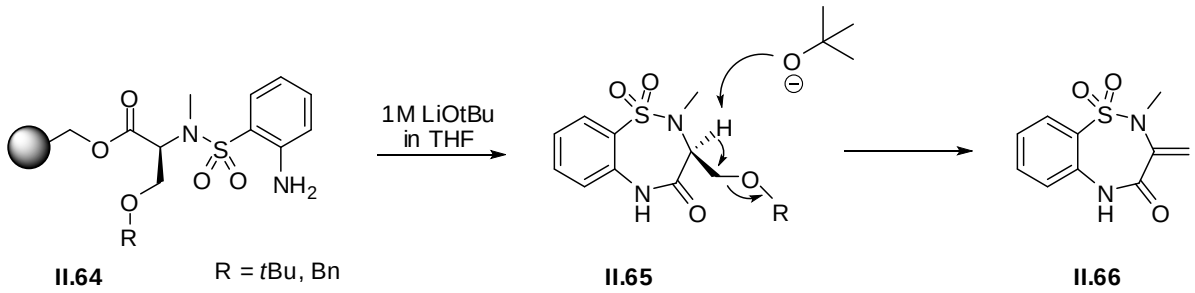
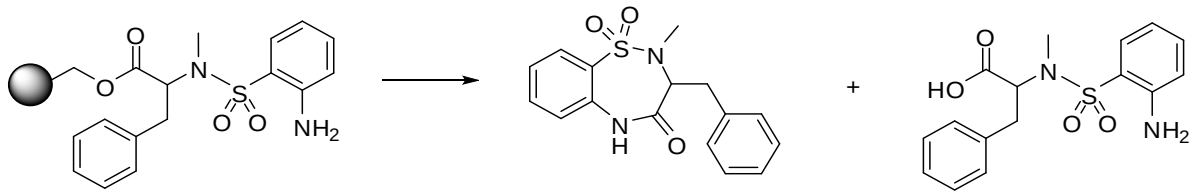


Figure II.18 *Base-induced elimination of the serine side chain*

2.1.3.6 RING CLOSURE IN ACIDIC CONDITIONS

As mentioned earlier, literature examples were published in which ring closure could be induced with a mild acid such as AcOH. Performing the ring closure in the presence of AcOH has some advantages compared to the ring closure with lithium *tert*-butoxide. For example after cyclization, the filtrate containing the product can be easily evaporated under reduced pressure leaving only the desired product in the flask. Also, the stereocenter at C_3 would probably not be affected by the presence of AcOH, yielding a final product which is enantiomerically pure (*vide infra*). Another positive feature of this approach is that the elimination problem associated with serine as building block could probably be avoided. A number of tests based on literature procedures were therefore conducted on ring closing precursor **II.63**, as described in *table **II.6***.



II.63 **II.7** **II.67**

ENTRY	SOLVENT/ACID	TEMP	TIME	RESULT
A	50/50 DCE/AcOH	RT	16 h	no product
B	20/80 DCE/AcOH	60°C[a]	30 min	no product
C	20/80 DCE/AcOH	100°C[a]	15 min	**II.67** + trace **II.7**
D	20/80 DCE/AcOH	100°C[a]	30 min	**II.67**
E	50/50 THF/AcOH	100°C[a]	15 min	**II.67**
F	90/10 DCE/TFA	RT	2 h 30 min	**II.67** + trace **II.7**
G	80/20 DCE/TFA	RT	6 h	**II.67**
H	80/20 DCE/TFA	RT	21 h	**II.67**
I	50/50 THF/HCOOH	100°C[a]	15 min	**II.67**

[a] = microwave heating applied

Table II.6 *Test reactions of the ring closure in acidic conditions*

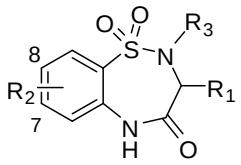
The first tests using acetic acid in different concentrations, solvents and at elevated temperatures (microwave heating) induced no cyclization/release reaction at all, only small amounts of the corresponding cleaved carboxylic acid were found. Increasing the strength of the acid applying formic acid or TFA also didn't afford the desired compounds, only increased amounts of carboxylic acid were detected. To avoid this premature cleavage from the resin, we decided to switch from Wang resin to the less acid sensitive hydroxymethyl-polystyrene (HM-PS). This solid support is the hydroxylated analog of Merrifield resin, so acid induced ring cleavage can only be performed with very strong acids such as HF or TFMSA. Also, the formed ester linkage is more electrophilic compared to the ester linkage in Wang resin, making this resin better suited for the attack of the aniline nitrogen. A new round of tests was performed on this resin, with the focus on TFA as ring closing catalyst (*table **II.7***).

ENTRY	SOLVENT/ACID	TEMP	TIME	RESULT
A	95/5 DCE/TFA	60°C[a]	30 min	**II.67**
B	80/20 DCE/TFA	60°C[a]	30 min	**II.67**
C	80/20 DCE/TFA	60°C[b]	30 min	**II.67**
D	50/50 DCE/TFA	60°C[b]	30 min	**II.67** + trace **II.7**
E	50/50 THF/TFA	60°C[b]	30 min	**II.67**
F	50/50 THF/TFA	100°C[b]	30 min	**II.7** + trace **II.67**
G	80/20 THF/TFA	100°C[b]	30 min	**II.7** + **II.67**
H	50/50 THF/TFA	80°C[b]	30 min	**II.7** + **II.67**

[a] = microwave heating, [b] = microwave heating with constant cooling (Powermax method)

Table II.7 *Test reactions of the ring closure in acidic conditions using HM-PS as solid support*

The first tests with DCE as a solvent yielded only traces of the carboxylic acid and none of the final products. By changing the solvent to THF however, suddenly peaks of ring closed product appeared in the LC-MS chromatogram. Heating the resin to 100° for 30 min in a 50/50 mixture of THF and TFA (entry F) seemed to give the best results, and these conditions were applied for the synthesis of a small library. Finally, 11 compounds were prepared using this method, as presented in *table **II.8***.



II.7

PRODUCT	R_1	R_3	R_2 7	R_2 8	YIELD
ab	iBu	Bn	H	H	12%
ac	iBu	2-(N-morpholino)ethyl	H	H	10%
o	Bn	Me	Cl	H	2%
r	Bn	Me	Br	H	10%
c	Bn	Me	H	H	10%
ad	Bn	Bn	H	H	22%
g	Bn	2-(N-morpholino)ethyl	H	H	9%
ae	H	Me	H	H	42%
af	H	CH_2Bn	H	H	47%
ag	H	iBu	H	H	32%
ah	H	$C_{10}H_{21}$	H	H	10%

[a] Yields are measured after purification and based upon the initial resin loading

Table II.8 *2,3-Dihydro-1,2,5-benzothiadiazepin-4(5H)-one-1,1-dioxides via ring closure using acidic conditions*

To check if our products were really cyclized on-resin and were not cleaved first and then ring closed in solution, a test reaction was performed by treating some cleaved carboxylic acid **II.67** under the same acidic conditions. To our surprise, the carboxylic acid **II.67** in our reaction mixture was converted quantitatively to the ring closed product. So seemingly, it was possible to cyclize the released ring closing precursor **II.67** in solution. The question then was whether these acidic conditions were also sufficient to cleave ring closing precursor from the solid support. Therefore, product **II.36** (precursor before nitro reduction) was treated under these strong acidic conditions and the filtrate analyzed. Indeed, the released carboxylic acid was present in the filtrate, hereby confirming the statement that the ring closing reaction could also consist of a premature cleavage and a consecutive ring closure in solution.

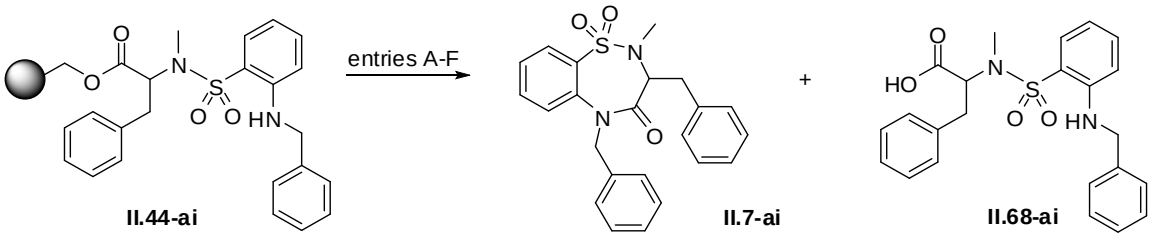
The combination of the quite harsh conditions, the lower yields of this method compared to the base-induced cyclization/release of analogous compounds and the fact that this method did not imply a real cyclization/release reaction made this method less attractive than the base induced ring closure. The

base-induced cyclization/release was therefore used as the method of choice for the synthesis of the 2,3-dihydro-1,2,5-benzothiadiazepin-4(5*H*)-one-1,1-dioxides **II.7**.

2.1.3.7 RING CLOSURE OF N_5-ALKYLATED COMPOUNDS

After synthesizing a first library of N_5-unsubstituted benzothiadiazepines using lithium *tert*-butoxide in THF, it was considered that the same conditions would also induce ring closure of the N_5-alkylated analogs. The secondary aniline nitrogen should be somewhat more nucleophilic compared to the primary aniline nitrogen, which should affect the ring-closing reaction positively. Of course, the increased steric hindrance would now also play an important role.

When applying these conditions on **II.44-ai**, no trace of the ring closed product **II.7-ai** could be detected (*table **II.9***, entry A). Therefore, some tests using elevated temperatures or a stronger base such as sodium hydride were performed (*table **II.9***, entries B and E) but these attempts were also unsuccessful. Base-induced ring closure failed, so we tried applying our optimized acidic conditions performed under microwave irradiation (entry D). This was no success either, leading to only traces of carboxylic acid **II.68-ai** and N_5-unsubstituted ring closed product.



ENTRY	CONDITIONS	RESULT
A	1 M LiOtBu in THF, rt, 30 min - 4 h	no product
B	1 M LiOtBu in THF, 60°C, MW, 30 min	no product
C	DMF, 80°C, MW, 30 min	no product
D	THF/TFA 50/50, 100°C, MW, 30 min	carboxylic acid **II.68-ai**
E	2 eq NaH, THF, 20 h	no product
F	5 eq 2-pyridone, THF, 60°C, MW, 16 h	no product

Table II.9 *Test conditions for the ring closure towards N_5-alkylated 2,3-dihydro-1,2,5-benzothiadiazepin-4(5H)-one-1,1-dioxide **II.7-ai**.*

One last option that was tested for this strategy was the application of the nucleophilic catalyst 2-pyridone **II.75** (*figure **II.19***). This catalyst had already been used for the ring closure in solution of pyrrole-annulated benzothiadiazpines **II.70** starting from precursor **II.69** (*figure **II.19-A***). Generally, it is known for accelerating the rate of aminolysis of esters **II.71**, because of its capacity to act simultaneously as a hydrogen donor and acceptor[187], in this way stabilizing the transition state **II.73** (*figure **II.19-B***). But unfortunately, this approach also did not lead to the ring closed product **II.7-ai**.

[187] Melander, C; Horne, D. A. *J. Org. Chem.* **1997**, *62*, 9295-9297.

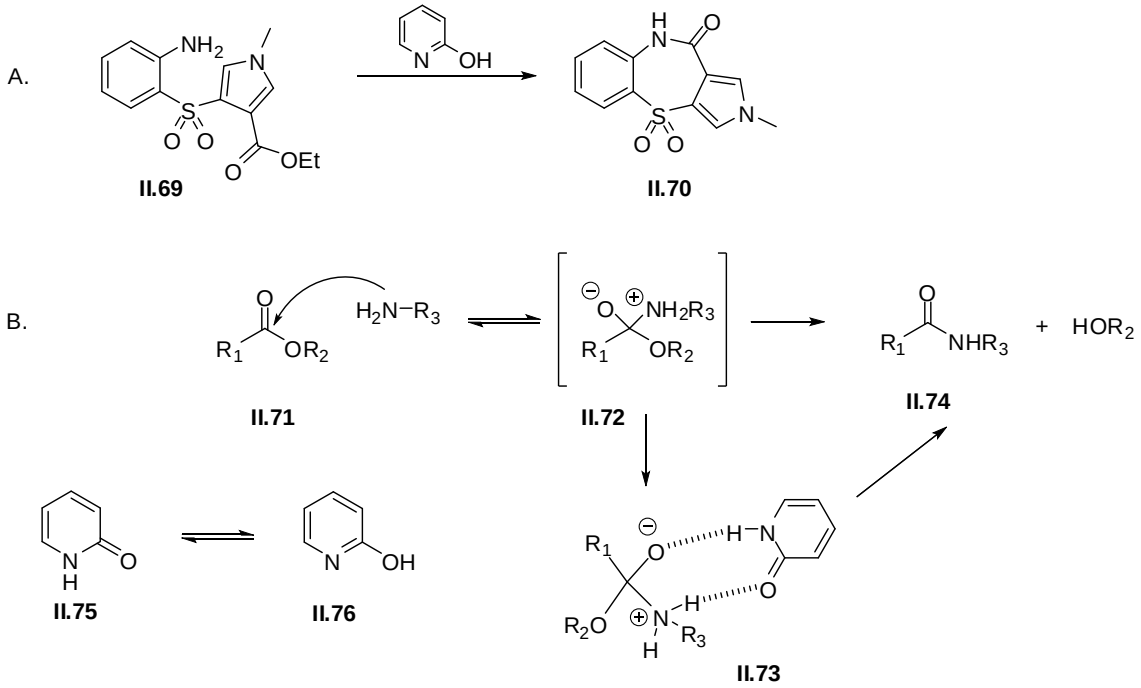


Figure II.19 A. *Example of the use of 2-pyridone as a catalyst* ***B.*** *Catalytic effect of 2-pyridone in aminolysis*

Because nor basic nor acidic conditions could induce ring closure of **II.44-ai**, it was assumed that steric hindrance was responsible for the failing cyclization reaction. Seemingly, the nitrogen of the secondary aniline moiety has difficulties reaching the ester carbonyl in a suitable way for lactam formation, even with small side chains. Therefore, we decided to change the strategy from cyclization/release to on-resin cyclization for these N_5-alkylated compounds. In this way, the carboxylic acid could be activated, making it probably easier to induce the ring closing reaction. This method is described in the next section.

2.2 SYNTHESIS VIA THE ON-RESIN CYCLIZATION STRATEGY

2.2.1 RETROSYNTHETIC OVERVIEW

Obviously, the last step in this strategy consists of the cleavage of the benzothiadiazepinone **II.7** from the solid support (*figure **II.20***). The crucial step however, is the ring closure by lactam formation towards benzothiadiazepinone **II.77**, which can now be triggered by activating the carboxylic acid of **II.78**. This precursor is built up by reacting a nosyl type building block **II.9** with a fluorenylmethyl protected α-amino acid **II.80** coupled on a formylated solid support **II.79**.

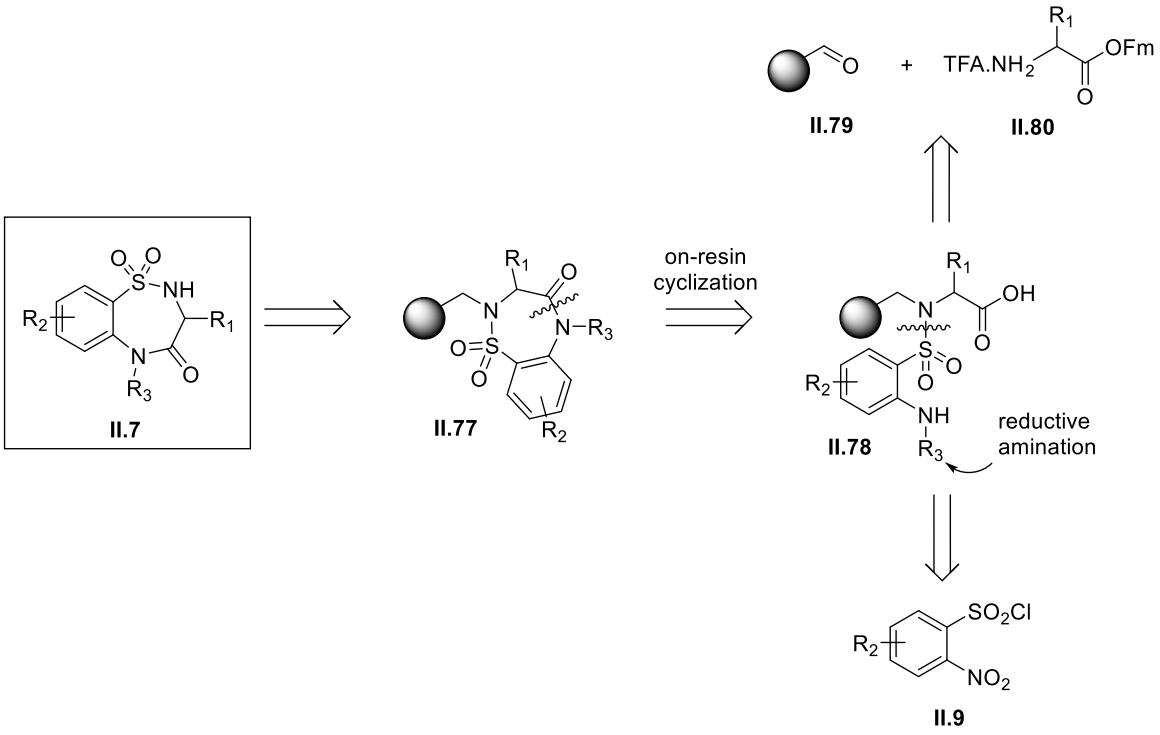


Figure II.20 *Retrosynthetic overview of the on-resin cyclization strategy for the 2,3-dihydro-1,2,5-benzothiadiazepin-4-one-1,1-dioxides*

2.2.2 CARBOXYLIC ACID ACTIVATION

The main advantage of the on-resin cyclization strategy is the possibility to activate the carboxylic acid moiety as during a classic peptide coupling reaction. Generally, this consists of transforming the carboxylic hydroxyl group into a good leaving group as in **II.82**, so the amine **II.83** can readily attack this reactive center and form peptide **II.84** (*figure **II.21***). A plethora of methods and reagents is available for the formation of a peptide bond on-resin[188] nowadays, but new coupling reagents with improved properties are still developed for difficult cases. Amide bond formation with secondary amines for example is known to be tedious on solid phase[189], even with all the known methods for activation at hand[190].

[188] El-Faham, A.; Albericio, F. *Chem. Rev.* **2011**, *111(11)*, 6557-6602.
[189] Angell, Y. M.; García-Echevarria, C.; Rich, D. H. *Tetrahedron Lett.* **1994**, *35(33)*, 5981-5984.
[190] Montalbetti, C. A. G. N.; Falque, V. *Tetrahedron* **2005**, *61(46)*, 10827-10852.

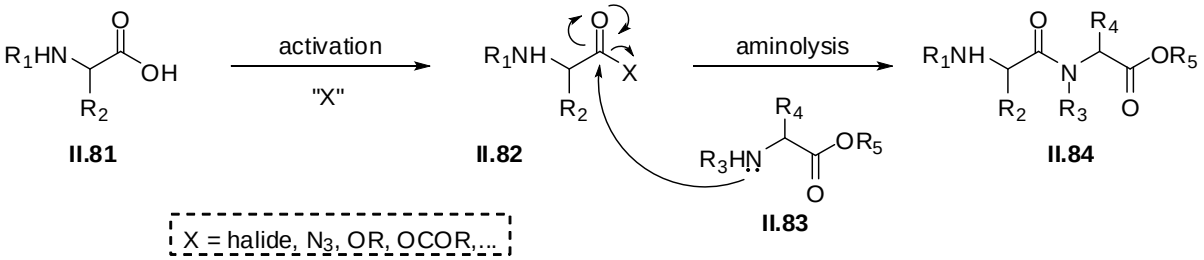


Figure II.21 *Classic mechanism for the peptide coupling reaction*

One of the first efficient reagents for coupling N-methylated amino acids was the phosphonium salt BrOP[191] (**II.85**), but this reagent yields the toxic HMPA (*figure **II.22***). Therefore, the safer and more efficient alternative PyBrOP[192] (**II.86**) was designed, in which the dimethylamino groups were replaced by pyrrolidino groups. This reagent was followed by the potent 1-hydroxy-7-azabenzotriazole additives and reagents such as HOAt (**II.87**), HATU (**II.88**) and PyAOP (**II.89**), which also proved valuable in the coupling of N-methylated amino acids. The reason for their superior coupling efficiencies compared to HOBt-derived reagents is the nitrogen atom at the 7 position. This electron-withdrawing nitrogen increases the leaving group capacity of the O-acyl moiety and participates during coupling by a so called *neighboring group* effect, enhancing the amide bond formation via internal general base catalysis (**II.90**). Other powerful methods that have been described for this purpose are the formation of acid fluorides using TFFH[193] (**II.91**) and acid chlorides using triphosgene[194] (**II.92**).

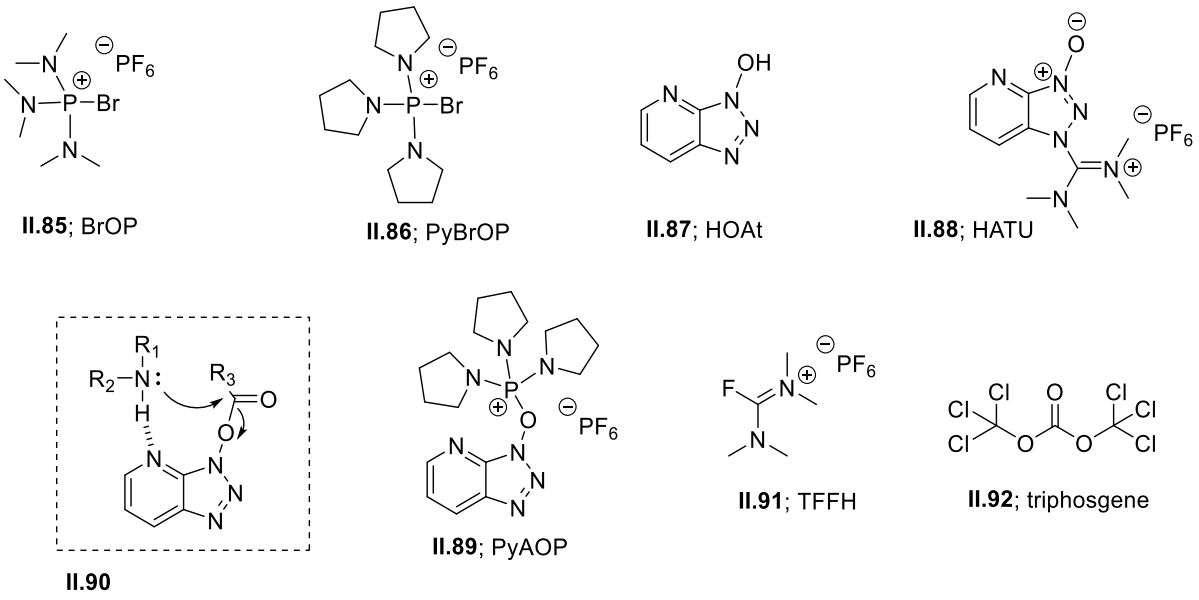


Figure II.22 *Coupling reagents and additives for N-methylated amino acids*

[191] Castro, B.; Dormoy, J. R. *Tetrahedron Lett.* **1973**, *14(35)*, 3243-3246.
[192] Coste, J.; Frérot, E.; Jouin, P.; Castro, B. *Tetrahedron Lett.* **1991**, *32(17)*, 1967-1970.
[193] Wenschuh, H.; Beyermann, M.; Winter, R.; Bienert, M.; Ionescu, D.; Carpino, L.A. *Tetrahedron Lett.* **1996**, *37(31)*, 5483-5486.
[194] Falb, E.; Yechezkel, T.; Salitra, Y.; Gilon, C. *J. Pept. Res.* **1999**, *53(5)*, 507–517.

2.2.3 FLUORENYLMETHYL PROTECTED α-AMINO ACIDS

An essential building block for the synthesis of benzothiadiazepinones applying the on-resin cyclization strategy, is a carboxyl protected α-amino acid **II.80**. The most obvious protective group for the carboxylic acid is the fluorenylmethyl protecting group, because of its mildly basic cleavage conditions and the possibility to use UV spectroscopy to determine the loading. These building blocks however were not commercially available, so they were synthesized in the lab starting from commercially available N-Boc protected α-amino acids in two short steps (*figure **II.23***). First, the Boc-protected amino acids **II.93** were reacted with 9-fluorenylmethanol applying a classic DIC/DMAP procedure to deliver the fully protected α-amino acids **II.94**. The reaction time is crucial for this esterification, because prolonged exposure of the fluorenylmethyl protected amino acids to DMAP leads to premature deprotection. The Boc-protecting group was then removed by stirring the amino acids in a 25% solution of TFA in CH_2Cl_2, which readily yielded the desired building blocks **II.80-(a-d)**. The yield of each synthesized building block is summarized in *table **II.10***.

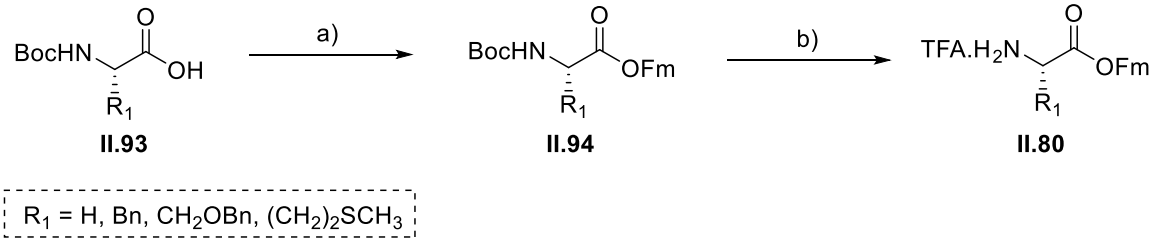


Figure II.23 *Synthesis of the fluorenylmethyl ester of α-amino acids **II.80-(a-d)***

PRODUCT	R_1	II.94	II.80
a	H	60%	91%
b	Bn	73%	90%
c	CH_2OBn	86%	64%
d	$(CH_2)_2SCH_3$	57%	83%

Table II.10 *Overview of the yields for building blocks **II.94** and **II.80***

2.2.4 SOLID SUPPORT

Because the application of the on-resin strategy requires the coupling of an amino acid via its N-terminal end, Wang resin is not suited for this approach. A brominated version of the Wang resin, resin **II.95**, seemed to be the most obvious choice, but problems with amino acid couplings due to *site-site* interactions described by Caroen made this resin not very attractive[195]. An alternative for this type of resins are the aldehyde functionalised resins, using a so called BAL approach[196] (BAL = Backbone Amide

[195] Caroen, J. (2012) *Ontwikkeling van een vastefasesynthesestrategie voor 1,2,3,4,5,6-hexahydro-1,5-benzodiazocine-2,6-dionen voor toepassing in combinatorische bibliotheken* Ph.D. Thesis Ghent University: Belgium.
[196] Boas, U.; Brask, J.; Jensen, K. J. *Chem. Rev.* **2009**, *109(5)*, 2092-2118.

Linker). This approach, introduced by Barany *et al.*[197], applied resin **II.96** with 5-(4-formyl-3,5-dimethoxyphenoxy)valeric acid as a linker and proved to be an excellent strategy for the synthesis of C-terminal-modified and cyclic peptides (*figure **II.24-A***).

For our synthesis, a modified version of the original BAL-linker was applied, namely the 4-(4-formyl-3-methoxy)phenoxybutyric acid or FMPB-linker (**II.98**). This linker is less acid-labile than the tris(alkoxy)-substituted original, less sterically hindered and also commercially available. It was coupled onto aminomethyl-polystyrene (AM-PS) using diisopropylcarbodiimide and 1-hydroxybenzotriazole in dichloromethane (*figure **II.24-B***). The coupling efficiency of this reaction was determined by a chloranil color test and was negative, so we could conclude that the reaction was quantitative.

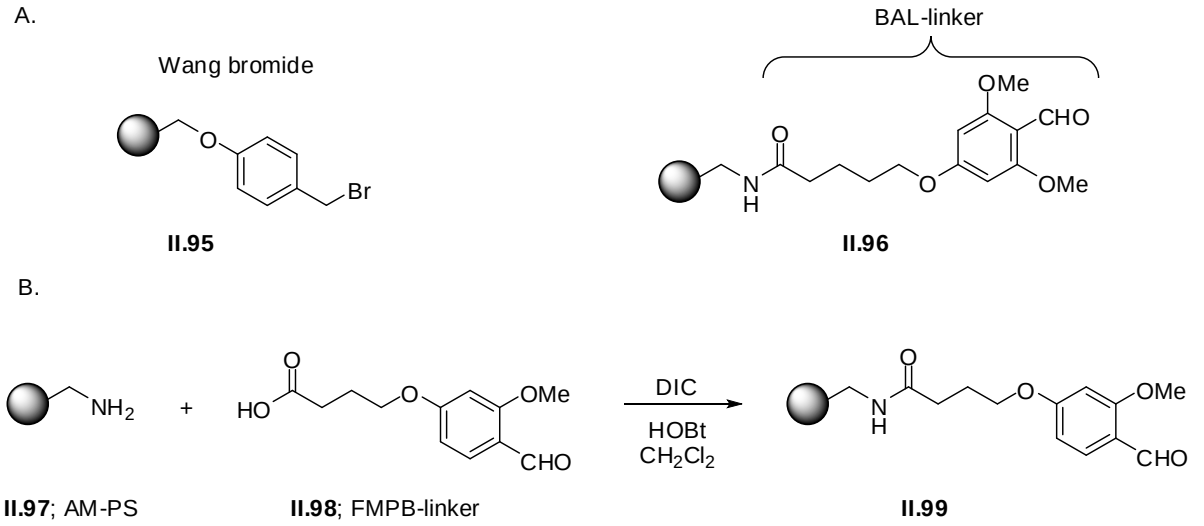


Figure II.24 A. *Wang bromide resin and the original BAL-resin* ***B.*** *Synthesis of FMPB-resin* ***II.99*** *using* ***II.98*** *and AM-PS (****II.97****)*

2.2.5 2,3-DIHYDRO-1,2,5-BENZOTHIADIAZEPIN-4(5*H*)-ONE-1,1-DIOXIDE SYNTHESIS

2.2.5.1 COUPLING OF THE α-AMINO ACIDS TO THE RESIN

Now that the FMPB-resin was ready for use, the coupling of the Fm-protected α-amino acid **II.53** could be performed. Therefore, a reductive amination using sodium triacetoxyborohydride in 1,2-dichloroethane was applied (*figure **II.25***). No acid had to be added during this reaction as a consequence of the use of the TFA salts of the corresponding amino acids. A quantitative Fm-test readily confirmed the coupling efficiencies of each building block onto the FMPB-resin after 16 h. The results are summarized in *table **II.11***. The low coupling yield for the glycine-derived building block **II.80-a** however was unexpected and could not be improved, even after a second or third treatment under the same coupling conditions.

[197] Alsina, J.; Jensen, K. J. Albericio, F.; Barany, G. *Chem. Eur. J.* **1999**, *5(10)*, 2787-2795.

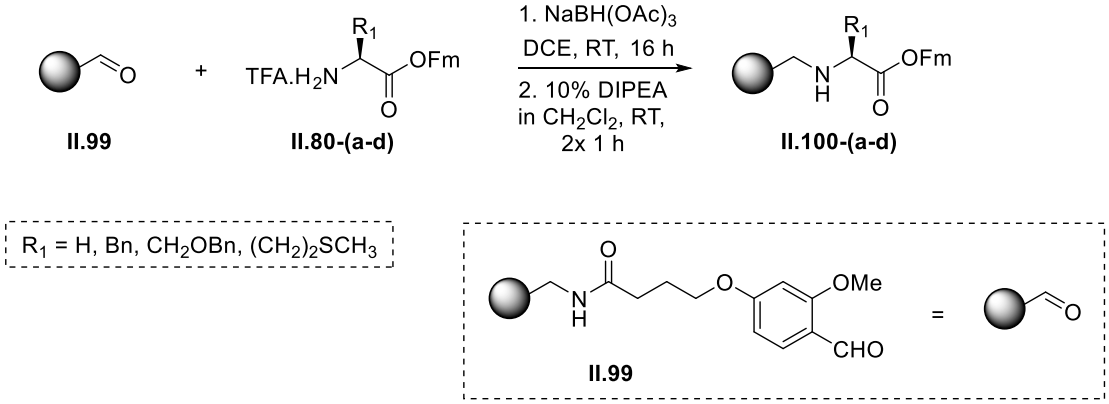


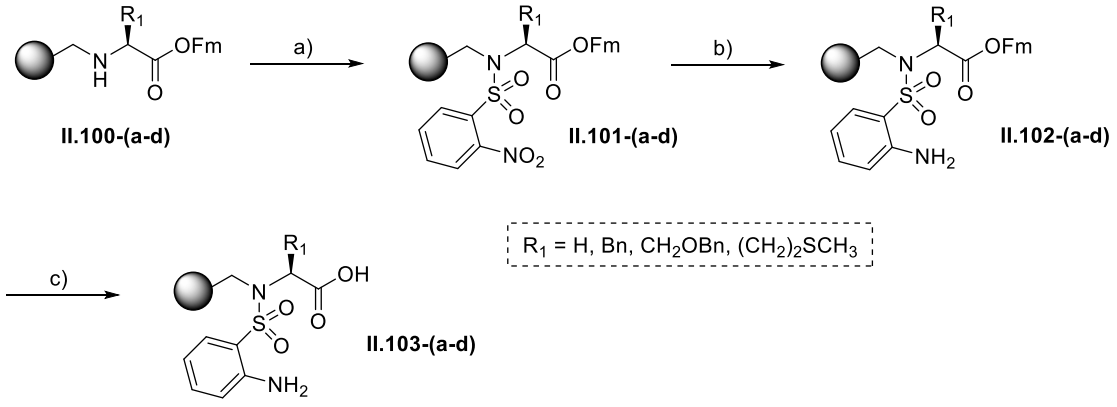
Figure II.25 *Coupling of the fluorenylmethylesters* ***II.80*** *onto the FMPB-resin* ***II.99***

PRODUCT	R_1	II.100
a	H	40%
b	Bn	91%
c	CH_2OBn	90%
d	$(CH_2)_2SCH_3$	79%

Table II.11 *Coupling yields of the α-amino acids to the FMPB-resin*

2.2.5.2 NOSYL INTRODUCTION, NITRO REDUCTION AND ON-RESIN CYCLIZATION

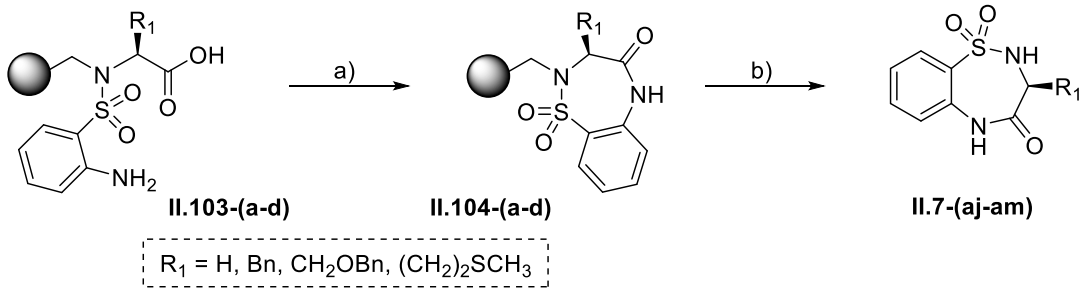
The next step in our synthesis was the attachment of nosylchloride onto the resin bound amino acid (*figure* ***II.26***). Although some sterical hindrance was expected because of the secondary amine, using identical conditions as during the cyclization/release strategy readily delivered the desired products **II.101-(a-d)**. The reduction of the nitro moiety also went smoothly applying the same reaction conditions as during the cyclization/release approach. Now, before continuing with the reductive N-alkylation, the ring closing reaction of compounds **II.103-(a-d)** could also be tried. Therefore, the fluorenylmethylester of **II.102-(a-d)** was removed using 4-methylpiperidine in DMF, resulting in ring closing precursors **II.103**-**(a-d)**.



a) *o*-NsCl, *sym*-collidine, CH_2Cl_2, RT, 2x 1 h b) $CrCl_2$, DMF/MeOH 9/1, RT, 2x 1 h c) i. 20% 4-Me-piperidine in DMF, RT, 2x 10 min ii. 10% AcOH in CH_2Cl_2, RT, 2x 1 h

Figure II.26 *Nosyl coupling, nitro reduction and fluorenylmethyl cleavage towards ring closing precursor* ***II.103-(a-d)***

A small scale test with compounds **II.103-(a-d)**, stirring the resin for 16 hours in the presence of diisopropylcarbodiimide and 1-hydroxybenzotriazole in a 50/50 mixture of dichloromethane/DMF, readily yielded the desired cyclized products **II.7-(aj-am)** after TFA-cleavage on small scale test reactions (*figure **II.27***). These conditions were then applied to a larger scale on the compounds with serine (because the synthesis of the serine analog was not successful applying the cyclization/release strategy) and phenylalanine as building blocks. After cleavage from the solid support, stirring the resin in a 95% TFA solution in water for 3 h, and purification using flash chromatography, the expected compounds were obtained in low yields (*table **II.12***). The LC-MS chromatogram of the crude product **II.7-al** after cleavage from the solid support is depicted in *figure **II.28***.



a) DIC, HOBt, CH_2Cl_2/DMF 50/50, RT, 16 h b) 95% TFA in water, RT, 3 h

Figure II.27 *On-resin cyclization and cleavage of 2,3-dihydro-1,2,5-benzothiadiazepin-4(5H)-one-1,1-dioxides **II.7-(aj-am)***

PRODUCT	R_1	YIELD
aj	H	<1%
ak	Bn	4%
al	CH_2OBn	6%
am	$(CH_2)_2SCH_3$	<1%

Table II.12 *2,3-Dihydro-1,2,5-benzothiadiazepin-4(5H)-one-1,1-dioxides obtained using the on-resin cyclization strategy*

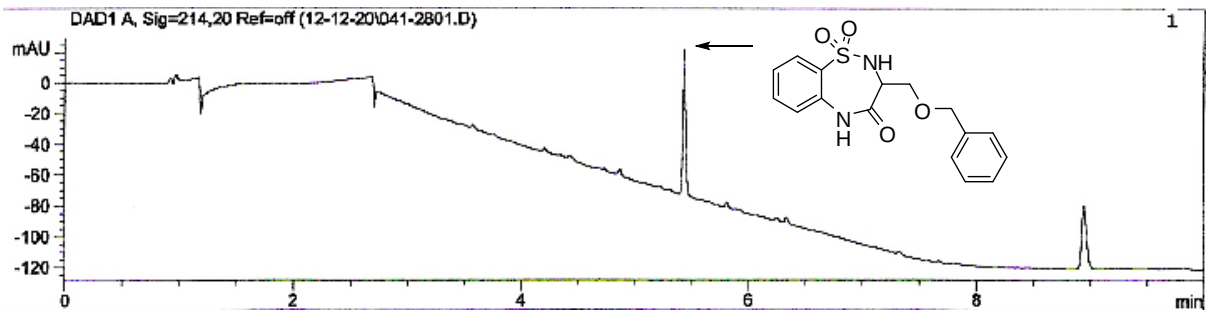


Figure II.28 *LC-MS chromatogram of the crude cyclized product **II.7-al** after cleavage from the solid support*

2.2.5.3 N_5-ALKYLATION

However, the original goal of this approach was the on-resin cyclization of N_5-alkylated compounds. To obtain these, the reductive alkylation conditions as described during the cyclization/release strategy were applied to **II.102**, using the aldehydes acetaldehyde, valeraldehyde and benzaldehyde (*figure **II.29***). A reaction time of 48 h seemed to be insufficient for complete conversion of the starting material, so this reaction was repeated once. The carboxylic acid of the N_5-alkylated product was then deprotected by shaking the resin twice in a mixture of 4-methylpiperidine in DMF, which readily delivered the ring closing precursor **II.105**.

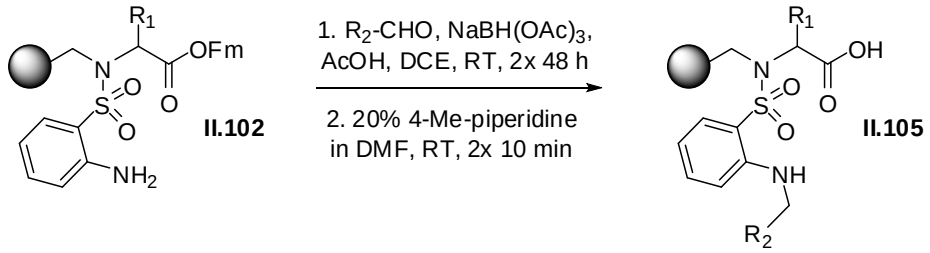


Figure II.29 *N_5-alkylation towards compound **II.105** using a reductive alkylation reaction*

2.2.5.4 RING CLOSURE

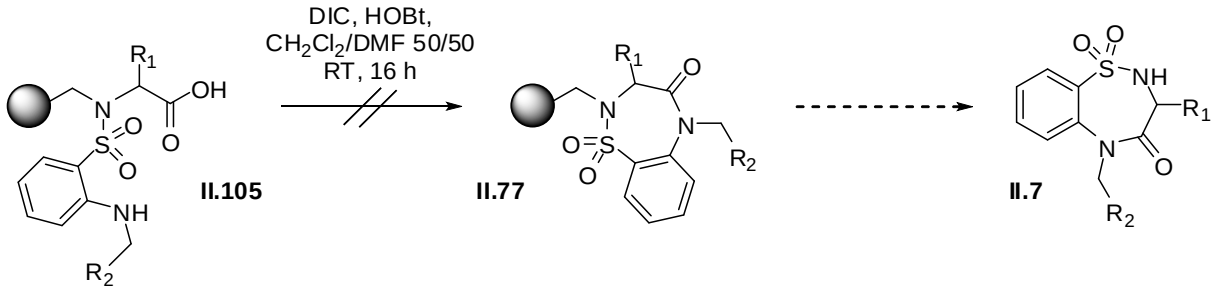
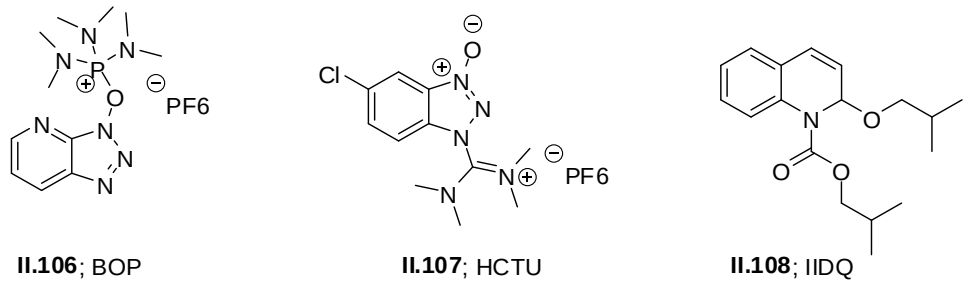


Figure II.30 *Ring closure and cleavage from the solid support*

The ring closure of these compounds **II.105** (*figure **II.30***) was then tested using the conditions that were applied for the successful on-resin cyclization of the non-N_5-alkylated analogs. But the DIC/HOBt combination failed to yield the desired benzothiadiazepinones **II.7**. Of course, due to the sterical hindrance of the secondary amino acid a more potent coupling reagent was indispensable. The coupling reagents that were tested were BOP[198] (**II.106**), HATU, HCTU[199] (**II.107**), PyBrOP and IIDQ[200] (**II.108**) (*figure **II.31***).

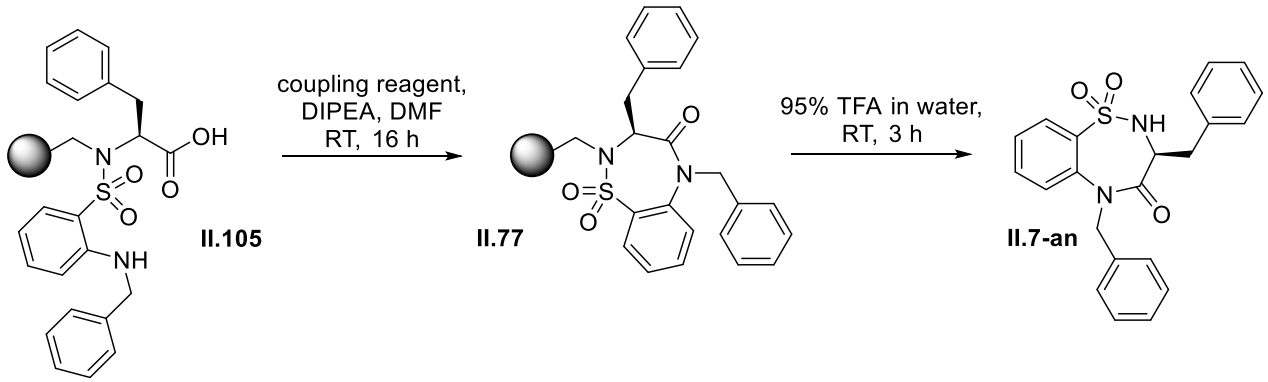
[198] Castro, B.; Dormoy, J. R.; Evin, G.; Selve, C. *Tetrahedron Lett.* **1975**, *16(14)*, 1219-1222.
[199] Hood, C. A.; Fuentes, G.; Patel, H.; Page, K.; Menakuru, M.; Park, J. H. *J. Pept. Sci.* **2008**, *14(1)*, 97-101.
[200] Kiso, Y.; Yajima, H. *J. Chem. Soc., Chem. Comm.* **1972**, *16*, 942-943.



II.106; BOP **II.107**; HCTU **II.108**; IIDQ

Figure II.31 *Applied coupling reagents in the tests for ring closure of N_5-alkylated compounds*

A small amount of resin **II.105** was reacted for 20 h with 5 equivalents of each coupling reagent and 10 equivalents of DIPEA in DMF. After cleavage from the solid support, the products were analysed by LC-MS. The results are summarized in *table **II.13***.



II.105 **II.77** **II.7-an**

ENTRY	REAGENT	RESULT
A	BOP	trace **II.7-an** + **II.105** + HOBt + **II.110**
B	HATU	trace **II.7-an** + **II.105** + HOAt + **II.110**
C	HCTU	trace **II.7-an** + **II.105** + 6-ClHOBt + **II.110**
D	PyBrOP	**II.7-an** + **II.110**
E	IIDQ	**II.105**

Table II.13 *Test reactions for the on-resin cyclization of N_5-alkylated benzothiadiazepinone **II.7-an***

The reaction with IIDQ only delivered the unreacted carboxylic acid (entry E), so no ring closure had taken place using this reagent. BOP, HATU and HCTU also delivered disappointing results, showing a small peak of unreacted carboxylic acid, a small peak of some residual 1-hydroxybenzotriazole and a significant peak of the 4-methylpiperdine amide **II.110** in the LC-chromatogram (entries A, B & C). The reaction with PyBrOP however, did yield the desired ring closed N_5-alkylated product **II.7-an**, with no trace of starting material but again with a significant peak of the 4-methylpiperidine amide (entry D). Apparently, after deprotection of the fluorenylmethylester, the released carboxylic acid forms a salt with 4-methylpiperidine (*figure **II.32***). This causes the formation of the 4-methylpiperidine adduct **II.109** during coupling. This problem could be resolved by shaking the resin twice for 1 h in a 10% solution of acetic acid in dichloromethane.

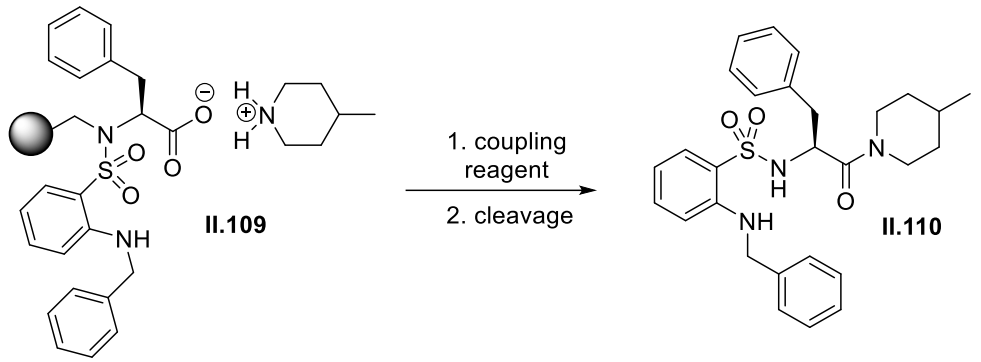


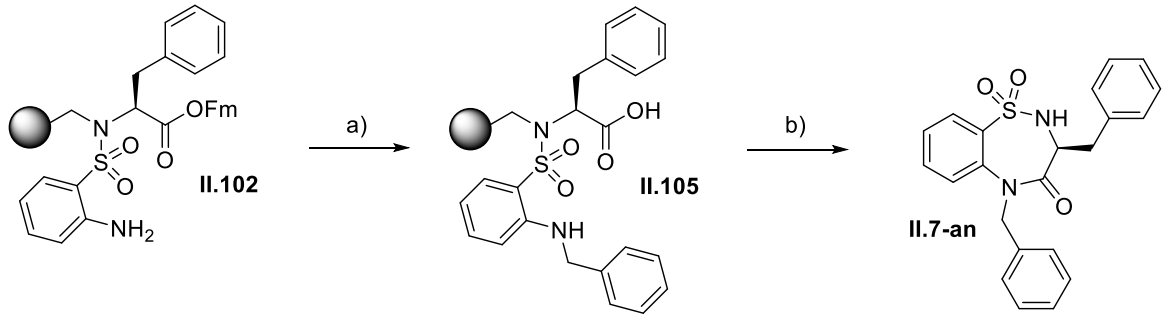
Figure II.32 *Formation of the 4-methylpiperidine amide byproduct during ring closure*

With these slightly adjusted conditions, some new test reactions were performed, of which the results are depicted in *table **II.14***. The results are quite similar compared to the first test, with PyBrOP as the best performing coupling reagent (entry D).

ENTRY	REAGENT	RESULT
A	BOP	trace **II.7-an** + trace **II.105** + HOBt
B	HATU	trace **II.7-an** + **II.105** + HOAt
C	HCTU	trace **II.7-an** + **II.105** + 6-ClHOBt
D	PyBrOP	**II.7-an** + trace **II.105**
E	IIDQ	**II.105**

Table II.14 *New test reactions for the on-resin cyclization of N_5-alkylated benzothiadiazepinone **II.7-an***

These conditions were then applied for the synthesis of compound **II.7-an** on a larger scale (0,3 mmol) (*figure **II.33***) and led successfully to the right product in low yield (4%).



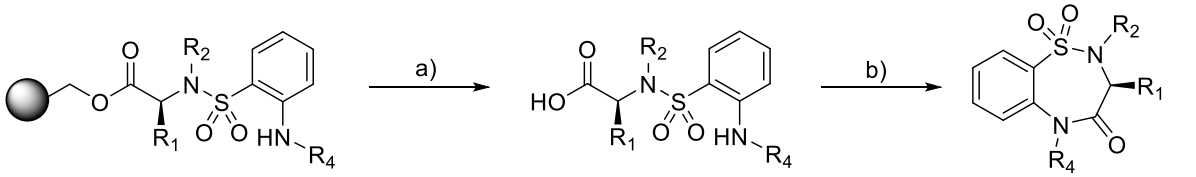
a) i. PhCHO, $NaBH(OAc)_3$, AcOH, DCE, RT, 2x 48 h ii. 20% 4-Me-piperidine in DMF, RT, 2x 10 min iii. 10% AcOH in CH_2Cl_2, RT, 2x 1 h b) i. PyBrOP, DIPEA, DMF, RT, 16 h ii. 95% TFA in H_2O, RT, 3 h

Figure II.33 *Deprotection, on-resin ring closure and cleavage from the solid support of product **II.7-an***

It can be concluded that the on-resin strategy made it possible to synthesize the desired N_5-alkylated compounds although in very poor yields. Moreover, the drawbacks associated with this approach such as the loss of a diversity point at the N_2-position, a quite expensive solid support and the non-commercially available building blocks make it certainly not the most practical one. A final strategy was therefore investigated, consisting of the ring closure in solution (*vide infra*).

2.3 RING CLOSURE IN SOLUTION

Yet another strategy for the ring closure of the N_5-alkylated benzothiadiazepinones was the cleavage of the cyclization/release ring closing precursor **II.108** from the solid support, followed by performing the cyclization reaction in solution (*figure **II.34***). In this way, the carboxylic acid **II.109** can be activated to induce lactam formation, as when applying the on-resin cyclization strategy. The cleavage from the solid support was performed by shaking resin **II.108** in a 95% TFA solution in water, readily delivering compounds **II.109**. After purification, these carboxylic acids **II.109** were ready for ring closure. The applied conditions for the ring closure were identical as for the on-resin cyclization, namely 5 equivalents of PyBrOP in the presence of 10 equivalents of diisopropylethylamine. These conditions also performed well in solution and were used successfully for the synthesis of four N_5-alkylated benzothiadiazepinones **II.7-(ao-ar)** (*table **II.15***).



a) 95% TFA in H_2O, RT, 3 h b) PyBrOP, DIPEA, DMF, RT, 4 h

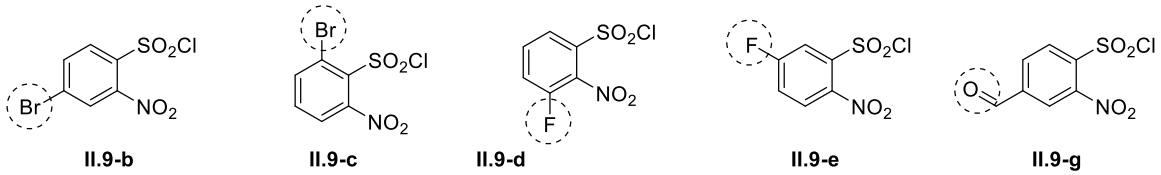
Figure II.34 *Ring closure in solution using the coupling reagent PyBrOP*

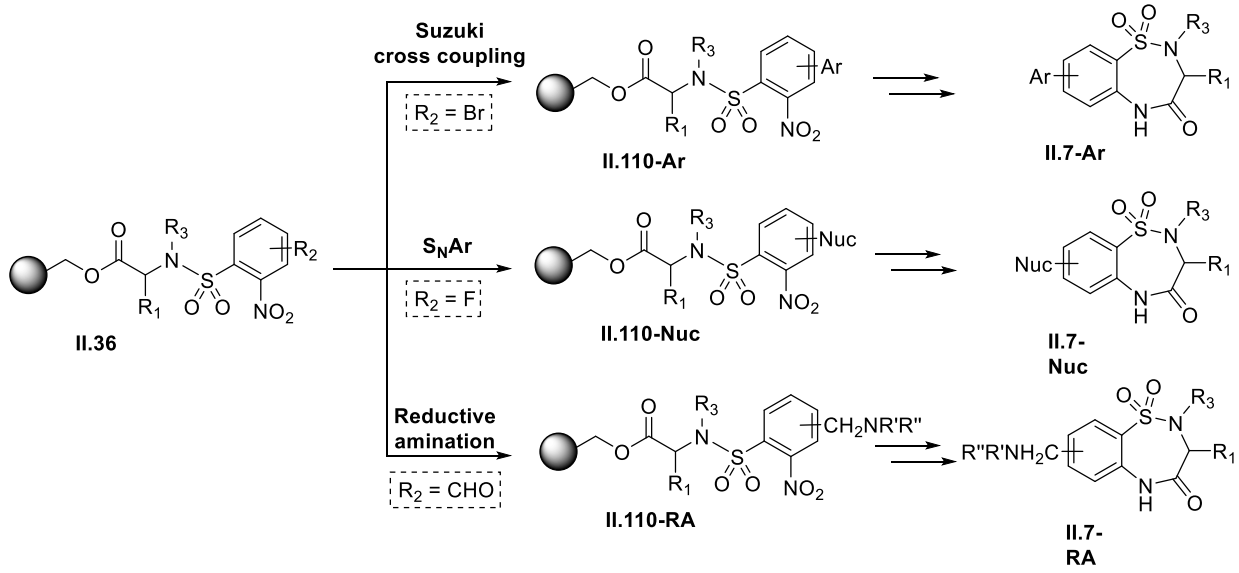
PRODUCT	R_1	R_2	R_4	YIELD II.109	YIELD II.7	Overall
ao	H	Me	*n*-pentyl	50%	60%	30%
ap	H	Bn	*n*-pentyl	32%	76%	24%
aq	H	Me	Bn	49%	72%	35%
ar	H	Bn	Bn	51%	65%	33%

Table II.15 *Yields of **r**ing closing precursors **II.109** after cleavage and 2,3-dihydro-1,2,5-benzothiadiazepin-4(5H)-one-1,1-dioxides **II.7-(ao-ar)** obtained by ring closure in solution after purification*

2.4 DERIVATIZATION OF THE BENZOTHIADIAZEPINONES VIA THE NOSYL BUILDING BLOCK

The synthesized substituted 2-nitrobenzenesulfonyl chlorides **II.9** were not only used as such, some of these building blocks allowed a further derivatization of the benzothiadiazepinones. The bromo-substituted building blocks for example could probably be used in a Suzuki cross coupling reaction. This further exploitation of the 2-nitrobenzenesulfonyl chloride building blocks **II.9** is discussed in the following part.





2.4.1 SYNTHESIS OF 7-ARYL-2,3-DIHYDRO-1,2,5-BENZOTHIADIAZEPIN-4(5*H*)-ONE-1,1-DIOXIDES

2.4.1.1 SUZUKI CROSS COUPLING REACTION

The introduction of the Suzuki coupling (or Suzuki-Miyaura coupling[201]) had a tremendous impact on organic synthesis[202]. Up till then, no real efficient method was known for the formation of biaryl compounds, despite their therapeutic value[203]. The most common used method was the Ullmann reaction, but the usually required elevated temperatures combined with the fact that it is not compatible with a number of substituents made this reaction not the most practical one. A Suzuki

[201] Miyaura, N.; Yanagi, T.; Suzuki, A. *Synth. Commun.* **1981**, *11(7)*, 513-519.
[202] a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95(7)*, 2457-2483 b) Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58(48)*, 9633-9695.
[203] The biphenyl framework is present in 4,3% of all known drugs: Hajduk, P. J.; Bures, M.; Praestgaard, J.; Fesik, S. W. *J. Med. Chem.* **2000**, *43(18)*, 3443-3447.

coupling on the contrary takes place under mild conditions and has a broad functional group compatibility. The use of boronic acids as substrates is also a positive feature because they are cheap, easy to handle and form easily removable byproducts.

The catalytic cycle of this reaction involves the oxidative addition of a Pd(0) species to the aryl halide **II.111**, followed by a transmetallation towards the double arylated complex **II.115**, involving the base-activated boronic acid **II.114**. A fast reductive elimination then readily delivers the coupled compound **II.116** and the regenerated palladium(0) complex[204](*figure **II.35***). The palladium catalyst originally consisted of tetrakis-(triphenylphosphine)palladium(0), but nowadays a whole series of catalysts is available for an array of different cross coupling reactions. The base and solvent applied for the Suzuki coupling also influence the reactivity and differ for each specific reaction.

In the field of cross coupling reactions, the use of microwave heating is an interesting application [205]. This efficient form of heating is useful in the area of cross coupling reactions because they tend to take quite some time when using conventional heating. Changing from conventional heating to microwave heating can decrease reaction times from several hours to less than 1 h[206].

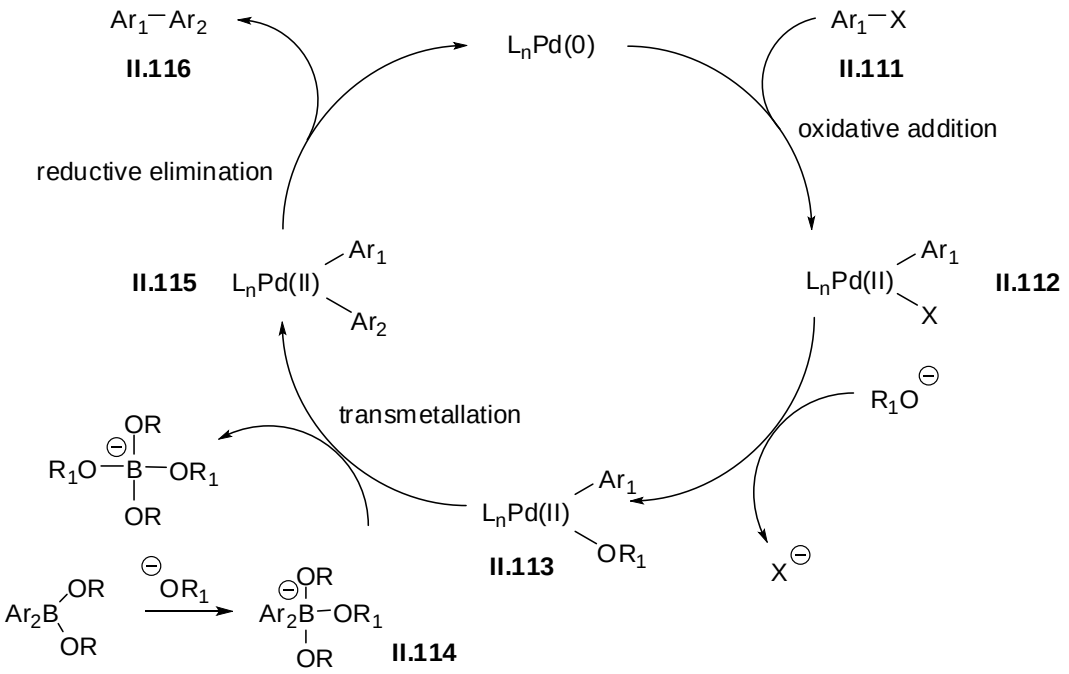


Figure II.35 *Catalytic cycle for the Suzuki-Miyaura cross coupling*

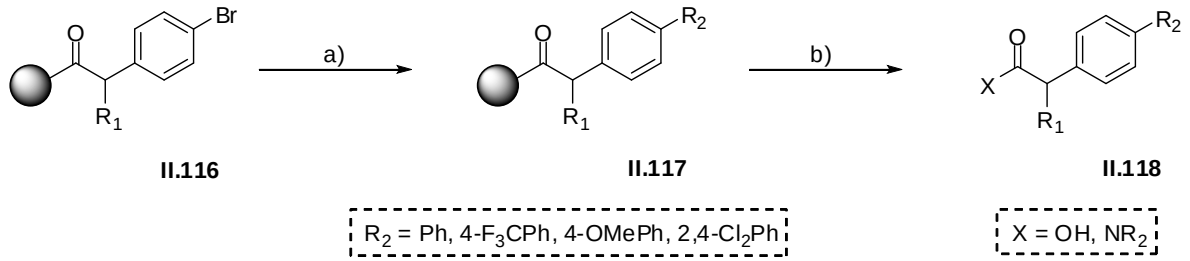
[204] Martin, R.; Buchwald, S. L. *Acc. Chem. Res.* **2008**, *41(11)*, 1461-1473.

[205] a) Larhed, M.; Hallberg, A. *J. Org. Chem.* **1996**, *61(26)*, 9582-9584 b) Kappe, C. O. *Angew. Chem. Int. Ed.* **2004**, *43(46)*, 6250-6284.

[206] a) Organ, M. G.; Mayer, S.; Lepifre, F.; N'Zemba, B.; Khatri, J. *Mol. Diversity* **2004**, *7(2)*, 211-227. b) Kaval, N.; Van der Eycken, J.; Caroen, J.; Dehaen, W.; Strohmeier, G. A.; Kappe, C. O.; Van der Eycken, E. *J. Comb. Chem.* **2003**, *5(5)*, 560-568. c) Wu, T. Y. H.; Schultz, P. G.; Ding, S. *Org. Lett.* **2003**, *5(20)*, 3587-3590.

2.4.1.2 SUZUKI REACTIONS ON SOLID PHASE

Because of its tremendous potential, the Suzuki coupling reaction was rapidly applied in the field of solid phase chemistry[207]. Ellman *et al.* for example demonstrated the use of the Suzuki reaction in the synthesis of a small library of substituted arylacetic acids **II.118** as potential cyclooxygenase inhibitors. He therefore refluxed the resin-bound bromophenyl activated **II.116** with a catalytic amount of $Pd(PPh_3)_4$ in the presence of a boronic acid, Na_2CO_3 in THF for 24-40 h (*figure **II.36***). Some other examples that implicated a Suzuki cross coupling reaction on solid phase, consist of the synthesis of biarylaldehydes [208], 2-arylindoles [209], biphenyltetrazoles [210], 1,4-benzodiazepine-2,5-diones [211] or arylpyrimidines[212].



a) $R_2B(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, THF, reflux, 24-40 h b) i. CH_2N_2 ii. OH^- or NR_2

Figure II.36 *Solid phase synthesis of substituted arylacetic acids by Ellman*

Next to these examples where the aryl halide is present on the solid support, the use of resin bound boronic acids[213] or solid phase palladium catalysts[214] has also been described. Because these were not used during this research, they will not be discussed further.

2.4.1.3 SYNTHESIS OF 7-ARYL-2,3-DIHYDRO-1,2,5-BENZOTHIADIAZEPIN-4(5H)-ONE-1,1-DIOXIDES

After coupling of the 4-bromo-2-nitrobenzenesulfonyl chloride **II.9-b** onto the solid support, the resin could already be arylated. However, we decided to perform the cross coupling reaction after Mitsunobu-Fukuyama alkylation of the sulfonamide, using compound **II.119** (*figure **II.37***). In this way, the acidic sulfonamide would not interfere during the cross coupling. We also did not postpone the cross coupling until after the reduction of the nitro moiety, because the aryl halide is preferably as electron deficient as possible for the oxidative addition.

---

[207] a) Frenette, R.; Friesen, R. W. *Tetrahedron Lett.* **1994**, *35(49)*, 9177-9180. b) Backes, B.; Ellman, J. A. J. *Am. Chem. Soc.* **1994**, *116(24)*, 11171-11172.
[208] Chamoin, S.; Houldsworth, S.; Kruse, C. G.; Bakker, W. I.; Snieckus, V. *Tetrahedron Lett*. **1998**, *39(24)*, 4179-4182.
[209] Zhang, H.-C.; Ye, H.; White, K. B.; Maryanoff, B. E. *Tetrahedron Lett.* **2001**, *42(29)*, 4751-4754.
[210] Yoo, S.-E.; Seo, J.-S.; Yi, K.-Y.; Gong, Y.-D. *Tetrahedron Lett.* **1997**, *38(7)*, 1203-1206.
[211] Boojamra, C. G.; Burow, K. M.; Ellman, J. A. *J. Org. Chem.* **1995**, *60(18)*, 5742-5743.
[212] Wade, J. V.; Krueger, C. A. *J. Comb. Chem.* **2003**, *5(3)*, 267-272.
[213] a) Hall, D. G.; Tailor, J.; Gravel, M. Angew. Chem. Int. Ed. 1999, 38(20), 3064-3067. b) Pourbaix, C.; Carreaux, F.; Carboni, B. *Org. Lett.* **2001**, *3(6)*, 803-805.
[214] a) Yang, J.; Li, P.; Wang, L. *Synthesis* **2011**, *2011(8)*, 1295-1301. b) Schweizer, S.; Becht, J.-M.; Le Drian, C. *Tetrahedron* **2010**, *66(3)*, 765-772. c) Schweizer, S.; Becht, J.-M.; Le Drian, C. *Org. Lett.* **2007**, *9(19)*, 3777-3780.

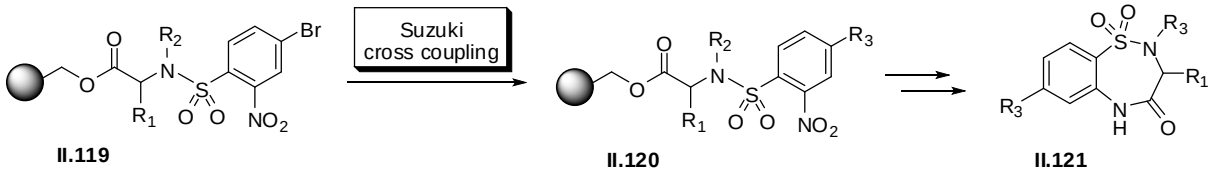


Figure II.37 *Suzuki cross coupling reaction towards arylated compound* ***II.121***

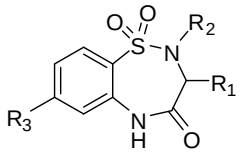
Hence, some tests were performed based on on-resin cross coupling reactions with similar substrates. All the tests were performed under microwave heating, the reaction conditions are depicted in *table* ***II.16***. As can be concluded from the first three tests (entries A,B & C), NMP is probably the best solvent for this reaction. Usually, this solvent is avoided for solution phase Suzuki couplings because of the difficult workup, but when using solid phase chemistry it can easily be filtered off. However, the reaction time of 3 min 30 s is too short to obtain a full conversion, even 10 min were insufficient to drive the reactions to completion (entries D & E). Almost full conversion of the starting material was obtained when stirring the resin 2x 30 min in the presence of 2,5 equivalents of Na_2CO_3 (entry F). An almost identical result was obtained by using 0,8 equivalents of K_2CO_3 after 30 min stirring (entry G). Based on these results, a test reaction was performed at a slightly higher reaction temperature of 80°C and with some more base (entry H). These reactions did deliver the desired results and were therefore used in all the following Suzuki cross coupling reactions. However, with electron deficient boronic acids such as 4-F_3CPhB$(OH)_2$, this reaction needed to be performed twice.

ENTRY	CONDITIONS	TIME	II.120/II.119
A	3 eq $PhB(OH)_2$, 0,2 eq $Pd(PPh_3)_4$, 1 eq $NaHCO_3$, NMP[a]	3 min 30 s	32/68
B	3 eq $PhB(OH)_2$, 0,2 eq $Pd(PPh_3)_4$, 1 eq $NaHCO_3$, DMF[a]	3 min 30 s	45/55
C	3 eq $PhB(OH)_2$, 0,2 eq $Pd(PPh_3)_4$, 1 eq $NaHCO_3$, DME[a]	3 min 30 s	86/14
D	3 eq $PhB(OH)_2$, 0,2 eq $Pd(PPh_3)_4$, 1 eq $NaHCO_3$, NMP[a]	10 min	52/48
E	3 eq $PhB(OH)_2$, 0,2 eq $Pd(PPh_3)_4$, 1 eq $NaHCO_3$, THF[a]	10 min	71/29
F	3 eq $PhB(OH)_2$, 0,2 eq $Pd(PPh_3)_4$, 2,5 eq Na_2CO_3, NMP[a]	2x 30 min	96/4
G	3 eq $PhB(OH)_2$, 0,2 eq $Pd(PPh_3)_4$, 0,8 eq K_2CO_3, NMP[a]	30 min	96/4
H	4 eq $PhB(OH)_2$, 0,2 eq $Pd(PPh_3)_4$, 2 eq K_2CO_3, NMP[b]	60 min	100/0

[a] Reactions A-G were performed in the MW at 70°C with constant cooling (Powermax method)
[b] Reaction H was performed in the MW at 80°C with constant cooling (Powermax method)

Table II.16 *Test reactions for the on-resin Suzuki cross coupling reaction*

After the reduction of the nitro group with chromium(II) chloride, these products could readily be ring closed applying the conditions for base-induced cyclization/release (see section *2.1.3.5*). A small library of 7-arylsubstituted benzothiadiazepinones **II.121-(a-j)** containing 10 members was synthesized, as depicted in *table* ***II.17***.



II.121-(a-j)

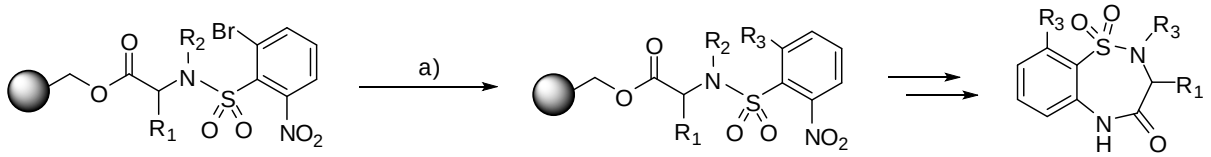
PRODUCT	R_1	R_2	R_3	YIELD[a]
a	H	Me	Ph	8%
b	Bn	Me	Ph	14%
c	Bn	Me	4-MeOPh	19%
d	iBu	Me	4-iBuOPh	39%
e	iBu	Me	3,5-F_2Ph	5%
f	N-Boc-3-indolylmethyl	Me	Ph	4%
g	iBu	Bn	Ph	22%
h	CH_2Ph(4-O*t*Bu)	iBu	3-thiophenyl	15%
i	CH_2Ph(4-OH)	iBu	3-thiophenyl	11%
j	CH_2Ph(4-O*t*Bu)	Me	2-MeOPh	21%

[a] Yields are measured after purification and based upon the initial resin loading

*Table **II.17** Overview of the 7-arylated 2,3-dihydro-1,2,5-benzothiadiazepin-4-one-1,1-dioxides **II.121***

2.4.2 SYNTHESIS OF 9-ARYL-2,3-DIHYDRO-1,2,5-BENZOTHIADIAZEPIN-4(5*H*)-ONE-1,1-DIOXIDES

When 2-bromo-6-nitrobenzenesulfonylchloride **II.9-c** was applied as building block, we had access towards the 9-aryl-1,2,5-benzothiadiazepin-4(5*H*)-one-1,1-dioxides **II.124**. It was assumed that the same cross coupling reaction conditions applied for the 7-arylated products **II.121** would also work for these compounds (*figure **II.38***). For these cross coupling reactions however, it turned out that we had to apply the conditions used for the difficult coupling of electron deficient boronic acids (2x 60 min reaction time). This is probably due to the more sterically hindered position of the bromo substituent, having the sulfonamide in *ortho*-position of the sulfonyl group.

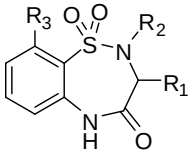


II.122 **II.123** **II.124**

a) $R_3B(OH)_2$, $Pd(PPh_3)_4$, K_2CO_3, NMP, 80°C, 2x 60 min

Figure II.38** Suzuki cross coupling reaction towards arylated compound **II.123

After performing the Suzuki cross coupling reaction with 3,5-F_2PhB$(OH)_2$, we also noticed a significant peak of the debrominated product in the LC-MS chromatogram. The slow coupling reaction probably favors the formation of the dehalogenated aryl. Three arylated compounds **II.123** were then reduced and ring closed using the base induced cyclization/release method, resulting in three 9-arylated 1,2,5-benzothiadiazepin-4(5*H*)-one-1,1-dioxides **II.125-(a-c)**, as depicted in *table **II.18***.



II.125

PRODUCT	R_1	R_2	R_3	YIELD[a]
a	iBu	Me	Ph	20%
b	iBu	Me	4-(OiBu)Ph	21%
c	iBu	Me	3-thiophenyl	22%

[a] Yields are measured after purification and based upon the initial resin loading

Table II.18 *Overview of the 9-aryl-2,3-dihydro-1,2,5-benzothiadiazepin-4(5H)-one-1,1-dioxides* ***II.125***

2.4.3 SYNTHESIS OF 8-ALKYLAMINO-2,3-DIHYDRO-1,2,5-BENZOTHIADIAZEPIN-4(5*H*)-ONE-1,1-DIOXIDES

2.4.3.1 NUCLEOPHILIC AROMATIC SUBSTITUTION (S_NAr)

Next to the common electrophilic aromatic substitution, aryls can also undergo nucleophilic aromatic substitution reactions. In this type of reaction, an aryl moiety exchanges one of its substituents with an incoming nucleophilic species. Generally, this reaction consists of a two-step mechanism as described in *figure* ***II.39***, but other mechanisms are known[215]. First, a nucleophile attacks compound **II.125** at the the ipso-position on the aromatic ring, with the formation of a *Meisenheimer complex* **II.126**. In a second step, aromaticity is restored by exclusion of the leaving group, resulting in the substituted product **II.127**. Evidence for this mechanism was the isolation of stable salts of these *Meisenheimer* (or *Meisenheimer-Jackson*) complexes[216].

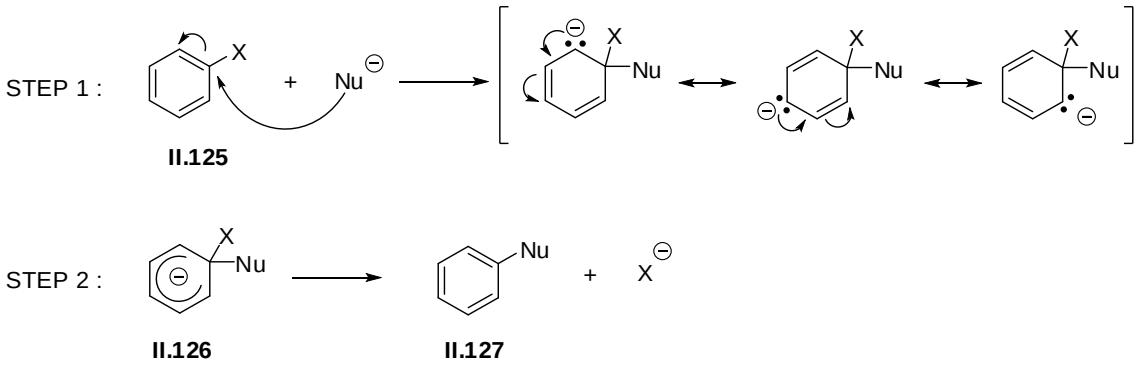


Figure II.39 *General mechanism of the SNAr reaction*

[215] Three other important mechanisms are described for nucleophilic aromatic substitutions: 1) An SN1 type mechanism: Himeshima, Y.; Kobayashi, H.; Sonada, T. *J. Am. Chem. Soc.* **1985**, *107(18)*, 5286-5288. 2) The benzyne mechanism: Bryce, M. R.; Vernon, M. *Adv. Heterocycl. Chem.* **1981**, *28*, 183-229. 3) The SN_R1 mechanism: Kim, J. K.; Bunnett, J. F. *J. Am. Chem. Soc.* **1970**, *92(25)*, 7463-7464. Another special type of reaction mechanism was described quite recently: Marquet, J.; Casado, F.; Cervera, M. Espín, M.; Gallardo, I.; Mir, M.; Niat, M. *Pure Appl. Chem.* **1995**, *67(5)*, 703-710.

[216] a) Meisenheimer, J. *Liebigs Ann. Chem.* **1902**, *323(2)*, 205-246 b) Jackson, C. L.; Gazzolo, F. H. *Am. Chem. J.* **1900**, *23*, 376-396.

The substituents on the aryl moiety are of utmost importance for the reactivity of the system. As the attack is performed by an electron-rich nucleophile at the ipso-position, SNAr reactions are accelerated by the presence of (strong) electron withdrawing groups in the *ortho*- or *para*-position of the leaving group (especially nitro groups). Next to this, the leaving group capacity also plays an important role in the SNAr reactions. Classic leaving groups used in aliphatic substitution reactions are as well good leaving groups in aromatic substitution reactions. However, the best leaving groups are the fluor and nitro moeity[217], which are not useful in aliphatic substitutions. This is also a proof that the S_NAr reaction follows a specific mechanism[218].

A famous example of the practical use of the nucleophilic aromatic substitution reaction is the protein sequencing reaction using the *Sanger reagent*, 1-fluoro-2,4-dinitrobenzene **II.128** (*figure **II.40***). The N-terminal amino acid is reacted with the Sanger reagent, delivering peptide **II.130**. The 2,4-dinitrobenzene moiety makes the final peptide bond sensitive to acid hydrolysis and can readily be cleaved delivering compound **II.131**, which can easily be identified. By repeating these amino acid cleavage steps, a complete peptide sequence can be determined[219].

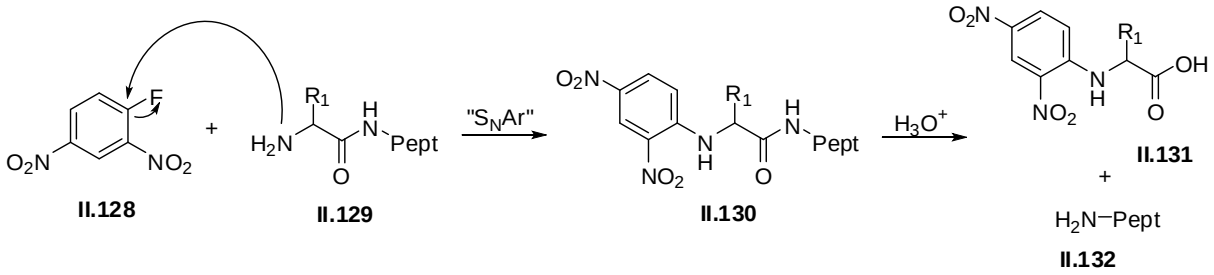


Figure II.40 *Use of the Sanger reagent for peptide sequencing*

Nucleophilic aromatic substitution reactions on solid phase have already been described several times, for instance in the synthesis of arylpiperazines[220], quinolones[221] and benzimidazoles[222].

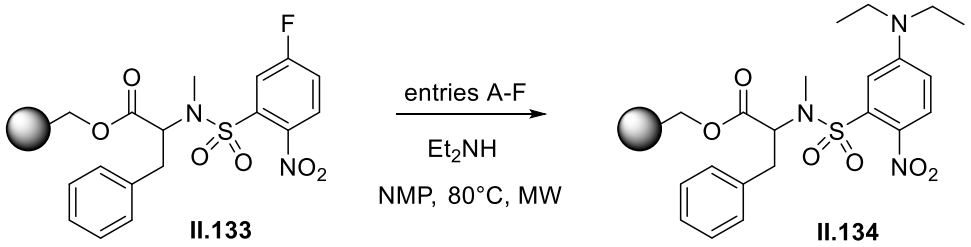
2.4.3.2 SYNTHESIS OF 8-ALKYLAMINO-2,3-DIHYDRO-1,2,5-BENZOTHIADIAZEPIN-4(5H)-ONE-1,1-DIOXIDES

The fluorine containing substrates **II.133**, obtained after coupling 5-fluoro-2-nitrobenzenesulfonyl chloride **II.9-e**, were probably susceptible to a nucleophilic aromatic substitution reaction, due to the presence of the nitro substituent in para position of the fluorine atom. Therefore, we tried to derive our own optimal reaction conditions to perform the nucleophilic aromatic substitution based on

[217] Beck, J. R. *Tetrahedron* **1978**, *34(14)*, 2057-2068.
[218] The first step of an S_NAr reaction is usually rate determining. The presence of strong -I substituents is therefore important, accelerating this first step.
[219] Sanger, F. *Biochem. J.* **1945**, *39(5)*, 507-515.
[220] Dankwardt, S. M.; Newman, S. R.; Krstenansky, J. L. *Tetrahedron Lett.* **1995**, *36(28)*, 4923-4926.
[221] MacDonald, A. A.; DeWitt, S. H.; Hogan, E. M.; Ramage, R. *Tetrahedron Lett.* **1996**, *37(27)*, 4815-4818.
[222] Phillips, G. B.; Wei, G. P. *Tetrahedron Lett.* **1996**, *37(28)*, 4887-4890.

literature precedents. Literature examples describe the use of dipolar aprotic solvents such as NMP[223] or DMF[224] as good solvents for these reactions. Most nucleophilic aromatic substitutions are also performed at elevated temperatures, from 50°C[225] to more than 100°C[226]. In some cases the addition of a base was required to catalyze the reaction[227], but when using amines this was not necessary. Reaction times varied from less than 5 min[228] to several days[229].

With these general directives, we tried to perform the nucleophilic aromatic substitution by heating the resin **II.133** in NMP to 80°C using microwave irradiation and by adding 20 equivalents of diethylamine (*figure **II.42***). The reaction progress was monitored at different reaction times. The results are summarized in *table **II.19***.

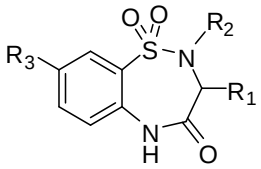


ENTRY	REACTION TIME	II.133/II.134
A	2 min 30 s	94/6
B	10 min	86/14
C	2x 10 min	74/26
D	30 min	44/56
E	2x 30 min	5/95
F	60 min	<1/>99

Table II.19 *Optimizing reaction times for the nucleophilic aromatic substitution towards **II.134***

There is a steady progress in conversion from 2 min 30 s towards 60 min, with full conversion after 60 min. These reaction conditions were used for the introduction of some other amines such as piperidine, morpholine or 4-methylpiperazine, which all delivered the desired aminated products. Only the reaction with dibenzylamine failed (<2% conversion), probably due to the steric hindrance of the two bulky benzyl moieties. After reduction and ring closure, a small library of four 8-aminoalkyl-1,2,5-benzothiadiazepin-4(5*H*)-one-1,1-dioxides **II.135-(a-g)** was obtained as depicted in *table **II.20***.

[223] Pelletier, J. C.; Chengalvala, M.; Cottom, J.; Feingold, I.; Garrick, L.; Green, D.; Hauze, D.; Huselton, C.; Jetter, J.; Wenling, K. Kopf, G. S.; Lundquist IV, J. T.; Mann, C.; Mehlmann, J.; Rogers, J.; Shanno, L.; Wrobel, J. *Bioorg. Med. Chem.* **2008**, *16(13)*, 6617-6640.
[224] Shaw, A. J.; Chen, Y.-R.; Tsai, C.-H. *Synth. Commun.* **2009**, *39(15)*, 2647-2663.
[225] Kim, J.-Y.; Boyer, F. E.; Choy, A. L.; Huband, M. D.; Pagano, P. J.; Vara Prasad, J. V. N. *Bioorg. Med. Chem. Lett*. **2009**, *19(2)*, 550-553.
[226] Buettelmann, B.; Roland, J.-R.; Knust, H.; Thomas, A. *PCT Int. Appl.* **2008**, WO 2009000662.
[227] Bernasconi, C. F.; de Rossi, R. H.; Schmid, P. *J. Am. Chem. Soc.* **1977**, *99(12)*, 4090-4101.
[228] Cherng, Y.-J. *Tetrahedron* **2000**, *56(42)*, 8287-8289.
[229] Brown, C. L.; Muderawan, I. W.; Young, D. J. *Synthesis* **2003**, *2003(16)*, 2511-2517.



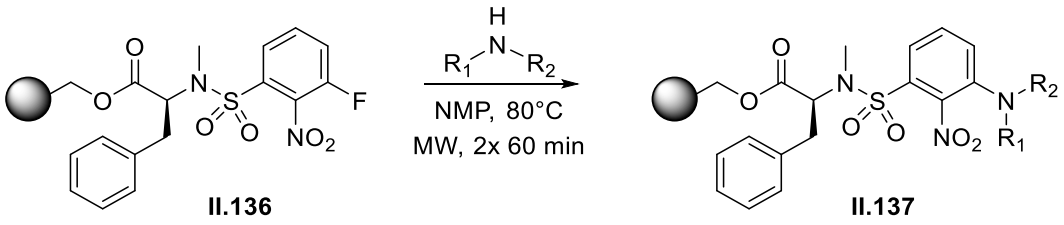
II.135

PRODUCT	R_1	R_2	R_3	YIELD
a	Bn	Me	$(CH_3CH_2)_2N$	18%
b	Bn	Me	N-cyclohexyl	43%
c	Bn	Me	N-morpholino	39%
d	Bn	Me	N-(4-Me-piperazinyl)	32%
e	iBu	Bn	N-cyclohexyl	39%
f	iBu	Me	N-(2-phenyl)Et	35%
g	(N-Boc)-indole-3-ylmethyl	Me	N-cyclohexyl	41%

Table II.20 *Overview of the synthesized 8-alkylamino-2,3-dihydro-1,2,5-benzothiadiazepin-4(5H)-one-1,1-dioxides* ***II.135***

2.4.4 SYNTHESIS OF 6-ALKYLAMINO-2,3-DIHYDRO-1,2,5-BENZOTHIADIAZEPIN-4(5*H*)-ONE-1,1-DIOXIDES

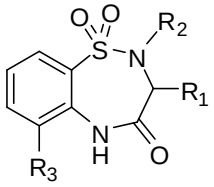
Next to 5-fluoro-2-nitrobenzenesulfonyl chloride we also coupled 3-fluoro-2-nitrobenzenesulfonyl chloride **II.9-d**, delivering resin bound compound **II.136**. These compounds were also submitted to a nucleophilic aromatic substitution reaction, using the same reaction conditions as described in the previous section. However, probably due to the steric influence of the nitro moiety the starting material was not completely converted after 1 h reaction time. Repeating the reaction a second time under the same conditions ultimately afforded the desired products **II.137** (*figure* ***II.41***).



II.136 **II.137**

Figure II.41 *Nucleophilic aromatic substitution towards compounds* ***II.137***

The reduction towards the ring closing precursors went smoothly, except for the analog that was substituted with propargylamine. Seemingly, the chromium(II) chloride partially reduced the alkyne group to the alkene. After ring closure, both compounds could however be separated by column chromatography. In this way, three 6-substituted benzothiadiazepinones **II.138-(a-c)** could be synthesized in total (*table* ***II.21***).



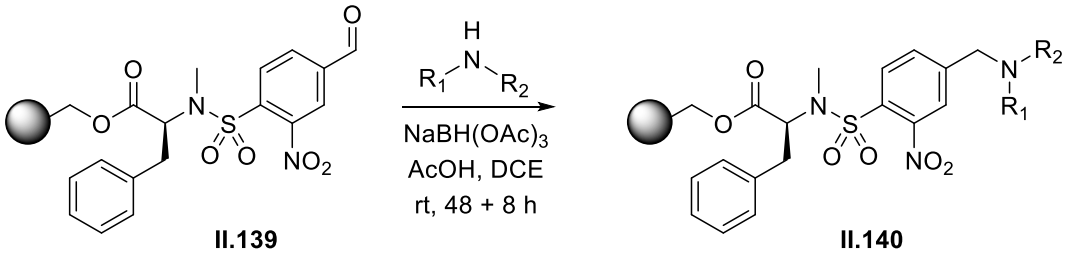
II.138

PRODUCT	R_1	R_2	R_3	YIELD
a	Bn	Me	N-morpholino	12%
b	Bn	Me	NH-propargyl	7%[a]
c	Bn	Me	NH-allyl	10%[a]

[a] yield determined based on the initial loading of resin **II.36**

Table II.21 *Overview of the synthesized 6-alkylamino-2,3-dihydro-1,2,5-benzothiadiazepin-4(5H)-one-1,1-dioxides* ***II.138***

2.4.5 SYNTHESIS OF 7-ALKYLAMINOMETHYL-2,3-DIHYDRO-1,2,5-BENZOTHIADIAZEPIN-4(5*H*)-ONE-1,1-DIOXIDES

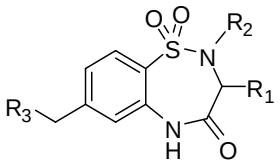


II.139 **II.140**

Figure II.42 *Reductive amination reaction on formyl substituted 2-nitrobenzenesulfonamides* ***II.139***

The introduction of the 4-formyl-2-nitrobenzenesulfonyl chloride building block **II.9-f**, delivering compound **II.139**, allowed us to perform a reductive amination (*figure* ***II.42***). Test reactions shaking the resin for 48h in the presence of 5 equivalents of an amine (benzylamine, morpholine or 4-methylpiperazine), 3 equivalents of sodium triacetoxyborohydride and 4 equivalents of acetic acid, resulted in an almost complete conversion to the aminated products. Full conversion towards compound **II.140** was eventually reached by repeating the same reaction conditions again for 8 h on these resins.

After reduction with chromium(II) chloride and the cyclization/release under basic conditions, three aminomethyl substituted benzothiadiazepinones **II.141-(a-c)** were obtained, as depicted in *table* ***II.22***



II.141

PRODUCT	R_1	R_2	R_3	YIELD
a	Bn	Me	NHBn	13%
b	Bn	Me	N-morpholino	20%
c	Bn	Me	N-(4-Me-piperazinyl)	22%

Table II.22 *Overview of the synthesized 2,3-dihydro-7-alkylaminomethyl-1,2,5-benzothiadiazepin-4(5H)-one-1,1-dioxides* ***II.141***

2.5 OPTICAL PURITY OF THE 2,3-DIHYDRO-1,2,5-BENZOTHIADIAZEPIN-4(5*H*)-ONE-1,1-DIOXIDES

2.5.1 RACEMIZATION DURING CYCLIZATION/RELEASE

After optimizing the cyclization/release reaction conditions, the enantiomeric purity of our final products was checked. Chiral analysis using chiral HPLC revealed that the intended final product **(S)-II.7-b**, built up from L-phenylalanine, was nearly racemic (20% *ee*). Because our products needed to be screened for biological activity, this was not considered as a problem. We therefore kept on synthesizing the products using the same protocol. However, there was a need for a synthesis protocol which could be used for the synthesis of the enantiopure compounds.

The problematic step causing the racemization is almost certainly the final ring closure. Indeed, the basic *tert*-butoxide ion probably caused the abstraction of the quite acidic C3 proton in the ring closed product **(S)-II.7-b**, leading to the loss of optical activity (*figure **II.43***). To confirm this, the optimized synthesis protocol was applied with isoleucine, an α-amino acid containing two stereocentra. A simple LC-MS analysis on an achiral column after each step could then detect the presence of an extra diastereomer, if epimerization had taken place at the C3 carbon. This test was negative for each synthetic step until after the reduction, so racemization had to occur during ring closure.

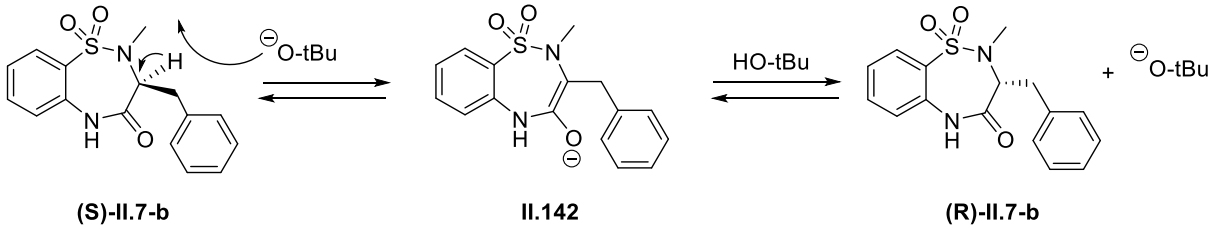
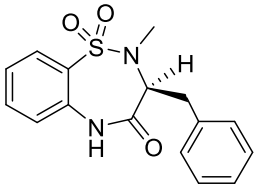


Figure II.43 *Racemization mechanism in basic conditions*

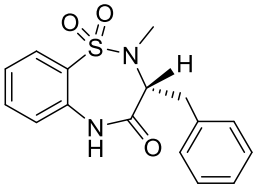
To solve this problem, we first tried to shorten the reaction time of the cyclization. We compared the yield and enantiomeric excess during the cyclization reaction of model compound **(S)-II.7-b** after 30 min, 1 h, 2 h and 4 h. Unfortunately, there was no amelioration of the optical purity of the product after shorter reaction times and the yields of the products were also dropping when applying shorter reaction times (*table **II.23***, entry A-D).

The most obvious solution however, was to avoid the use of base and to apply acidic conditions for ring closure. To our surprise, the products obtained under acidic cyclization conditions turned out to be not enantiomerically pure after ring closure neither (entry E). The harsh conditions for ring closure, 30 min in a 50/50 THF/TFA mixture at 100°C, were apparently sufficient to induce racemization. Indeed, in the literature, racemization under extreme acidic conditions has been described before[230], so yet another method had to be found.

[230] for example: a) Smith, G. G.; De Sol, B. S. *Science* **1980**, *207*, 765-767 b) Smith, G. G.; Reddy, G. V. *J. Org. Chem.* **1989**, *54(19)*, 4529-4535



(S)-II.7-b



(R)-II.7-b

ENTRY	TIME	CONDITIONS	(S)-II.7-b/(R)-II.7-b
A	30 min	1M LiOtBu in THF	41/59
B	1 h	1M LiOtBu in THF	40/60
C	2 h	1M LiOtBu in THF	45/55
D	4 h	1M LiOtBu in THF	40/60
E	30 min	50/50 THF/TFA	15/85

Table II.23 *Racemization ratios in different reaction conditions*

2.5.2 RACEMIZATION DURING RING-CLOSURE IN SOLUTION

As the on-resin cyclization approach was not really successful, the most obvious solution for this problem consisted in cleaving of the ring closing precursor from the solid support and then subsequently cyclizing this compound in solution. Because this strategy had already been optimized using N_5-alkylated products, this protocol could readily be used for the synthesis of an alanine containing benzothiadiazepinone **II.7-n** (*figure **II.44***). For comparison, this product was also ring closed using the basic conditions applied for the cyclization/release. After chiral analysis of the resulting compounds, we found that the ring closure in solution led to an almost enantiomerically pure product **(S)-II.7-n** (99% *ee*) while the cyclization/release reaction using lithium *tert*-butoxide resulted in a mixture of both enantiomers **(S)-II.7-n** and **(R)-II.7-n** (26% *ee*).

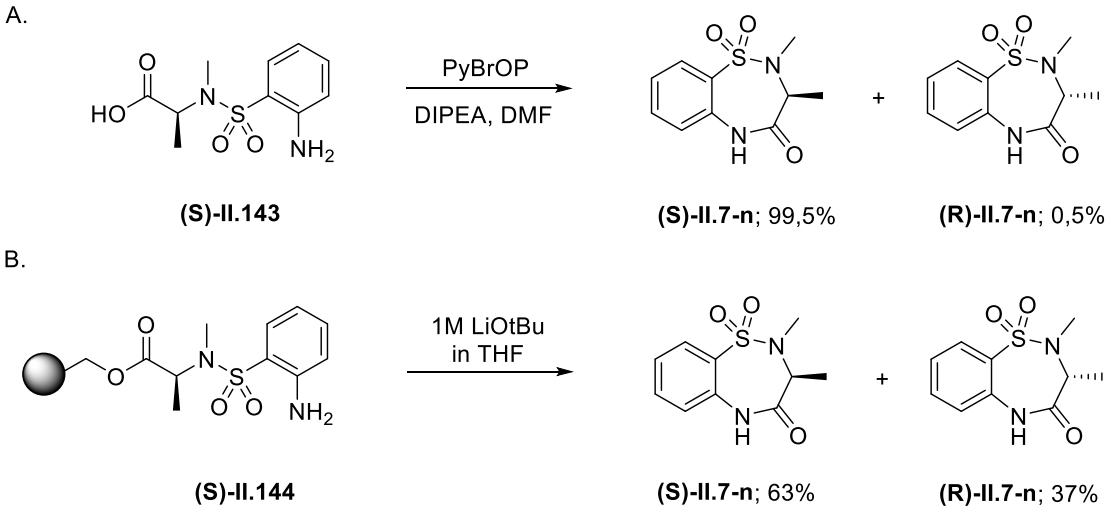
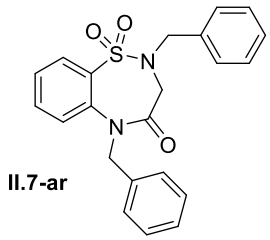


Figure II.44 *Overview of the racemization rates applying **A.** the ring closure in solution **B.** the cyclization/release strategy*

2.6 XRD-ANALYSIS

To attain some structural information about these scaffolds, a couple of them were crystallized and submitted to an XRD-analysis.

The crystal structure of 2,5-dibenzyl-1,2,5-benzothiadiazepin-4(5H)-one-1,1-dioxide **II.7-ar** is shown in figure **II.45-A**. The space group of this crystal is $p2_1/c$ and thus centrosymmetric. This means there are two enantiomers present in the crystal structure, although there is no stereocenter present in the molecule. Seemingly, the sulfonamide nitrogen acts like a stereocenter in its solid state form. This particular feature had already been described in literature for similar benzothiadiazepinones, as mentioned in the introduction (section 7.1). An overlay of both enantiomers is shown in *figure **II.45-B***.



II.7-ar

A. B.

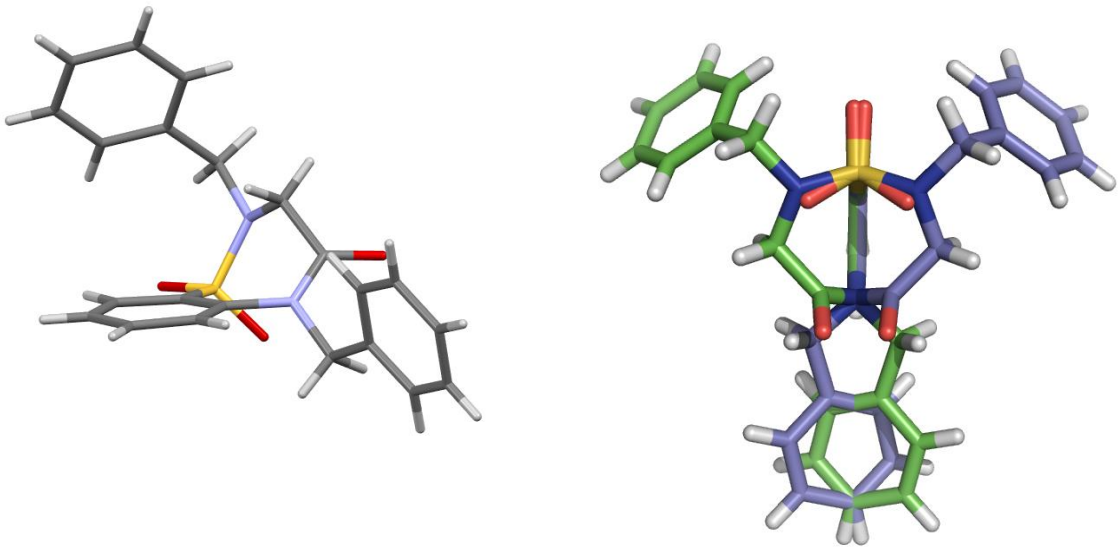
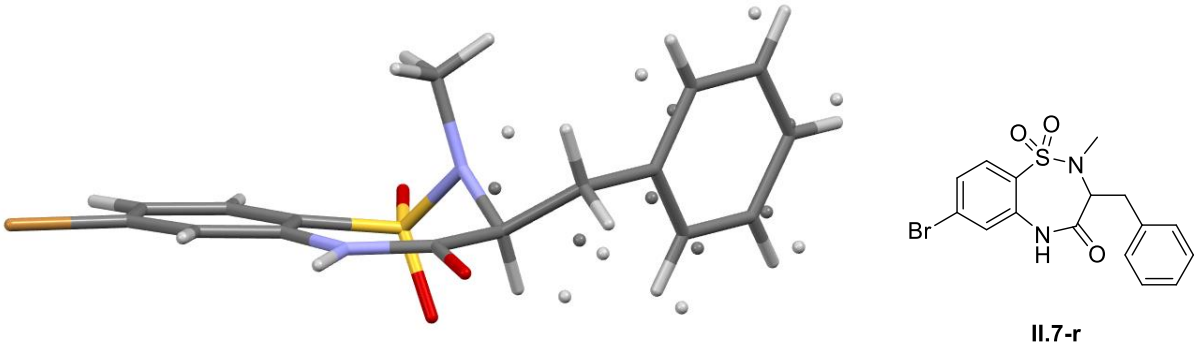


Figure II.45 A. *Crystal structure of 2,5-dibenzyl-1,2,5-benzothiadiazepin-4(5H)-one-1,1-dioxide **II.7-ar** **B.** Overlay of both enantiomers of **II.7-ar***

The crystal structure of 3-benzyl-7-bromo-2,3-dihydro-1,2,5-benzothiadiazepin-4(5*H*)-one-1,1-dioxide **II.7-r** is depicted in *figure **II.46***. As the previous crystal structure, it is characterized by the $p2_1/c$ space group and thus centrosymmetric. Now, the crystal consists of 4 stereoisomers, as both the N_2 and the

C_3-position are chiral centres[231]. An overlay of both N_2 epimers is shown in *figure **II.47 A***, while an overlay of both C_3 epimers is depicted on *figure **II.47-B***.

The most striking difference between the crystal structure of **II.7-r** and **II.7-ar** is the position of the C_3 carbon. In the case of **II.7-ar**, the C_3 atom is pointing out extremely high from the plane of the molecule, probably to aim the substituents on the N_2 and N_5-position in pseudo-equatorial positions. In the case of **II.7-r**, when a benzyl group is present on the C_3-position, the C_3 carbon remains in the plane of the molecule, pointing the benzyl group pseudo-equatorial. Now, the N_2 atom is lifted above the plane, probably because this situation results in less sterical hindrance and thus a lower energetic state.



II.7-r

Figure II.46 *Crystal structure of 3-benzyl-7-bromo-2,3-dihydro-1,2,5-benzothiadiazepin-4(5H)-one-1,1-dioxide **II.7-r***

A. B.

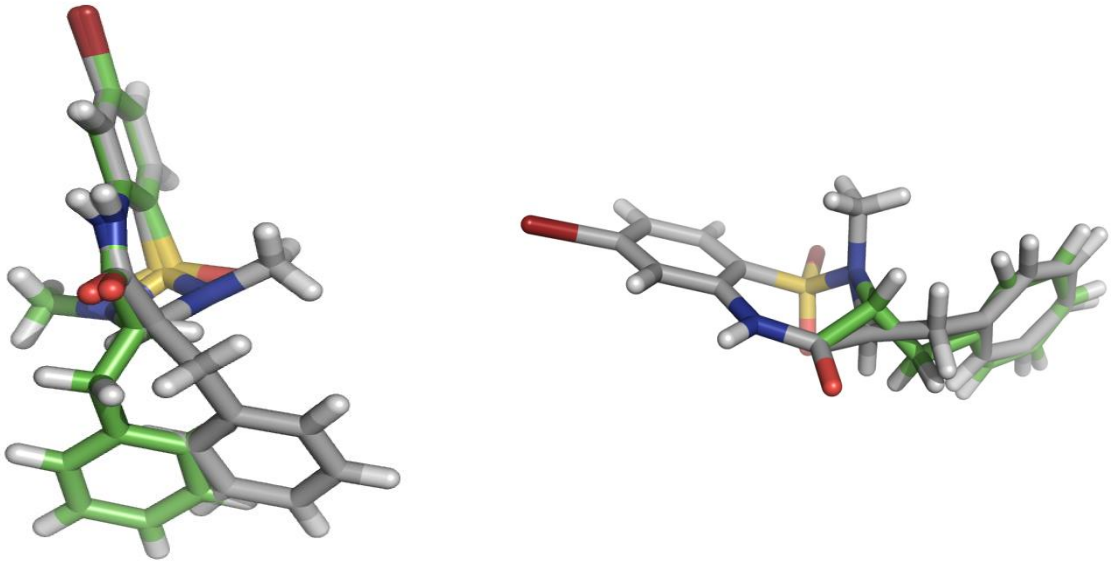
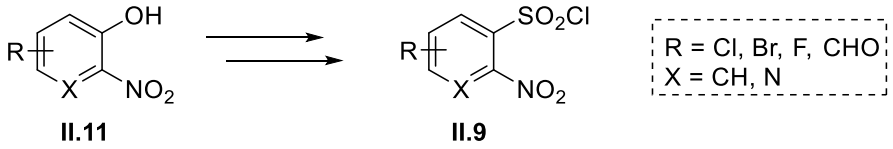


Figure II.47 A. *Overlay of both sulfonamide epimers of **II.7-r** **B.** Overlay of both C3 epimers of **II.7-r***

[231] Both the (3R) and (3S) enantiomer are present, as compound **II-7-r** was synthesized as its racemate.

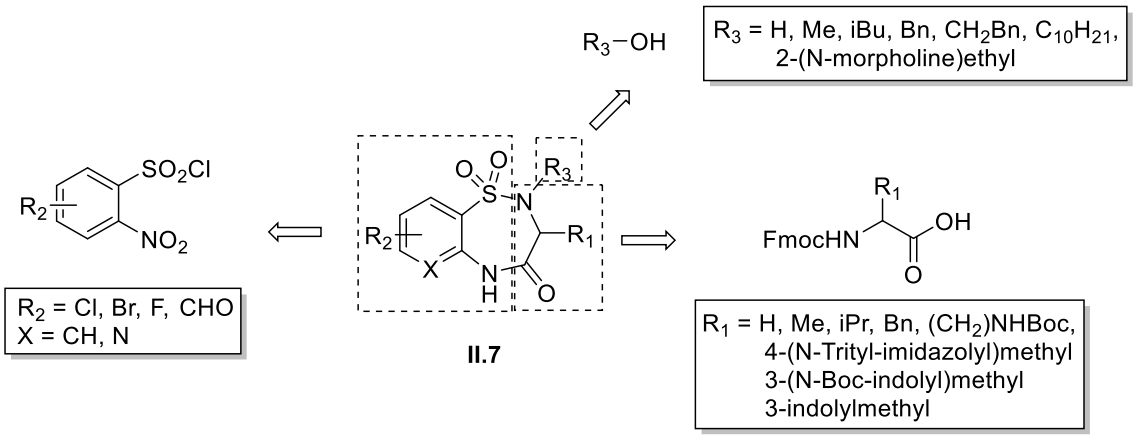
2.7 CONCLUSION

To synthesize the 2,3-dihydro-1,2,5-benzothiadiazepin-4(5*H*)-one-1,1-dioxides **II.7**, a solid phase strategy using a cyclization strategy was proposed first. An essential building block during this synthesis consisted of substituted 2-nitrobenzenesulfonyl chlorides **II.9**. A short synthetic route was devised towards these building blocks starting from commercially available 2-nitrophenols. This route successfully delivered eight 2-nitrobenzenesulfonyl chlorides **II.9-(a-h)** (10-79%), substituted on the four remaining positions on the benzene moiety.



II.11 **II.9**

With these building blocks in hand, the proposed synthetic route on solid phase was executed. Introducing different α-amino acids, nosyl buiding blocks **II.9-(a-h)** and alcohols, a first library of 2,3-dihydro-1,2,5-benzothiadiazepin-4(5*H*)-one-1,1-dioxides **II.7-(a-ah)** containing twenty-seven members (5-62%) diversified on three positions was synthesized. The final cyclization/release step was performed in basic conditions, leading to products with a high crude purity. The application of strong acidic conditions for the ring closure also led to the desired benzothiadiazepinones (11 members, 2-47%), but via a premature cleavage and subsequent cyclization in solution.



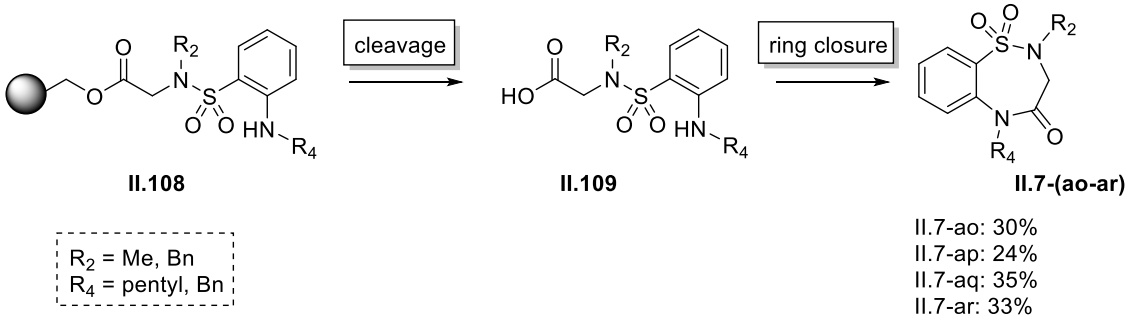
II.7

The introduction of a fourth point of diversity on the N_5-position using a reductive amination with different aldehydes also went smoothly, but led to problems concerning the ring closure. Nor the previously applied basic conditions nor the acidic conditions could induce the ring closure. The use of a strong base or the nucleophilic catalyst 2-pyridone also couldn't deliver the desired N_5-alkylated 2,3-dihydro-1,2,5-benzothiadiazepin-4(5*H*)-one-1,1-dioxides. Therefore it was decided to switch towards an on-resin cyclization strategy, which allowed the activation of the carboxylic acid for ring closure.

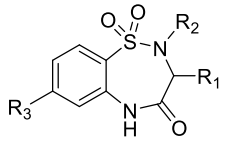
To execute this synthetic strategy, a fluorenylmethyl protected α-amino acid **II.80** is an essential building block. Applying a two-step protocol starting from Boc protected α-amino acids, four of these necessary building could be synthesized in good yields. A synthetic route towards the desired benzothiadiazepinones was then optimized and readily delivered the N_5-alkylated ring closing precursors **II.105**. Ring closure of these precursors could then be induced with the coupling reagent

PyBrOP, leading to the synthesis of four 2,3-dihydro-1,2,5-benzothiadiazepin-4(5*H*)-one-1,1-dioxides **II.7-(ak-an)**. The overall results of this strategy were however quite disappointing, combining low product yields (<6%) with the loss of one diversity point, so yet another strategy was investigated.

This strategy consisted of the cleavage of the ring closing precursor from the solid support, followed by a ring closure in solution. Four new N_5-alkylated ring closing precursors **II.108-(ao-ar)** were build up using the synthesis protocol applied for the cyclization/release strategy. After cleaving these from the solid support, they could readily be ring closed with the use of the coupling reagent PyBrOP **II.87**. This delivered four N_5-alkylated 2,3-dihydro-1,2,5-benzothiadiazepin-4(5*H*)-one-1,1-dioxides **II.7-(ao-ar)**.

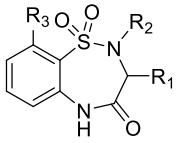


The introduction of functionalized 2-nitrobenzenesulfonyl chlorides **II.9-(b-f)**, allowed us to further differentiate the scaffold on positions 6, 7, 8 and 9. The bromo-substituted positions 7 and 9 were successfully submitted to an on-resin cross coupling reaction, delivering respectively ten 7-arylated and three 9-arylated benzothiadiazepinones **II.121-(a-j)** and **II.124-(a-c)**. The fluoro-substituted positions 6 and 8 were susceptible for a nucleophilic aromatic substitution reaction, which allowed the introduction of structurally different amines on the scaffold. This led to three 6-alkylaminobenzothiadiazepinones **II.135-(a-c)** and seven 8-alkylaminobenzothiadiazepinones **II.135-(a-g)**. The last modification consisted of a direct reductive amination on the formyl-substituted compounds, readily delivering three 7-alkylaminomethylated derivates **II-141-(a-c)**.



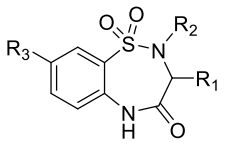
R_1 = H, iBu, Bn, CH_2Ph(4-OtBu), (N-Boc)-indole-3-ylmethyl
R_2 = Me, iBu, Bn
R_3 = Ph, 4-MeOPh, 4-iBuOPh, 3,5-F_2Ph, 3-thiophenyl, 2-MeOPh

II.121-(a-j)
yield: 4-39%



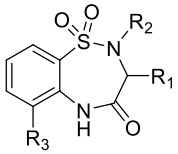
R_1 = iBu
R_2 = Me
R_3 = Ph, 4-iBuOPh, 3-thiophenyl

II.125-(a-c)
yield: 20-22%



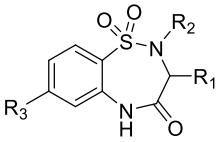
R_1 = iBu, Bn
R_2 = Me, Bn
R_3 = $(CH_3CH_2)_2$N, N-cyclohexyl, N-morpholino, N-(4-Me-piperazinyl) N-(2-phenyl)Et

II.135-(a-g)
yield: 18-43%



R_1 = Bn
R_2 = Me
R_3 = N-morpholino, NH-propargyl NH-allyl

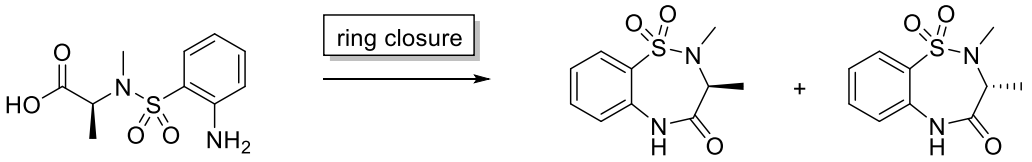
II.138-(a-c)
yield: 7-12%



R_1 = Bn
R_2 = Me
R_3 = NHBn, N-morpholino, N-(4-Me-piperazinyl

II.141-(a-c)
yield: 13-22%

The compounds obtained applying the cyclization/release strategy were not enantiomerically pure. Seemingly, the final cyclization in basic or strong acidic conditions caused racemization of the C_3 stereocenter. Because the compounds were synthesized for screening purposes this was not considered as a problem, but a racemization-free protocol would however be convenient. Therefore, as in the case of the N_5-alkylated products, the ring closing precursor **II.109** was cleaved off before ring closure and cyclization was performed in solution using PyBrOP. This readily delivered a nearly optical pure 2,3-dihydro-1,2,5-benzothiadiazepin-4(5*H*)-one-1,1-dioxide **(S)-II.7-n** (99% *ee*).



(S)-II.143

(S)-II.7-n; 99,5%

(R)-II.7-n; 0,5%

Two 2,3-dihydro-1,2-5-benzothiadiazepin-4(5*H*)-one-1,1-dioxides were also submitted to an XRD-analysis, delivering interesting structural information.

3 SYNTHESIS OF THE 1,2,5-THIADIAZEPAN-4-ONE-1,1-DIOXIDES

Our second target scaffold consisted of the 1,2,5-thiadiazepan-4-one-1,1-dioxides **II.145**. To obtain these 7-membered sulfonamide containing lactams, both a cyclization/release or an on-resin cyclization strategy could be devised. However, as with the benzothiadiazepinones, the cyclization/release strategy would be investigated first, keeping the on-resin cyclization strategy as a back-up in the case of synthetic problems when applying the first method.

3.1 SYNTHESIS VIA THE CYCLIZATION/RELEASE STRATEGY

3.1.1 RETROSYNTHETIC OVERVIEW

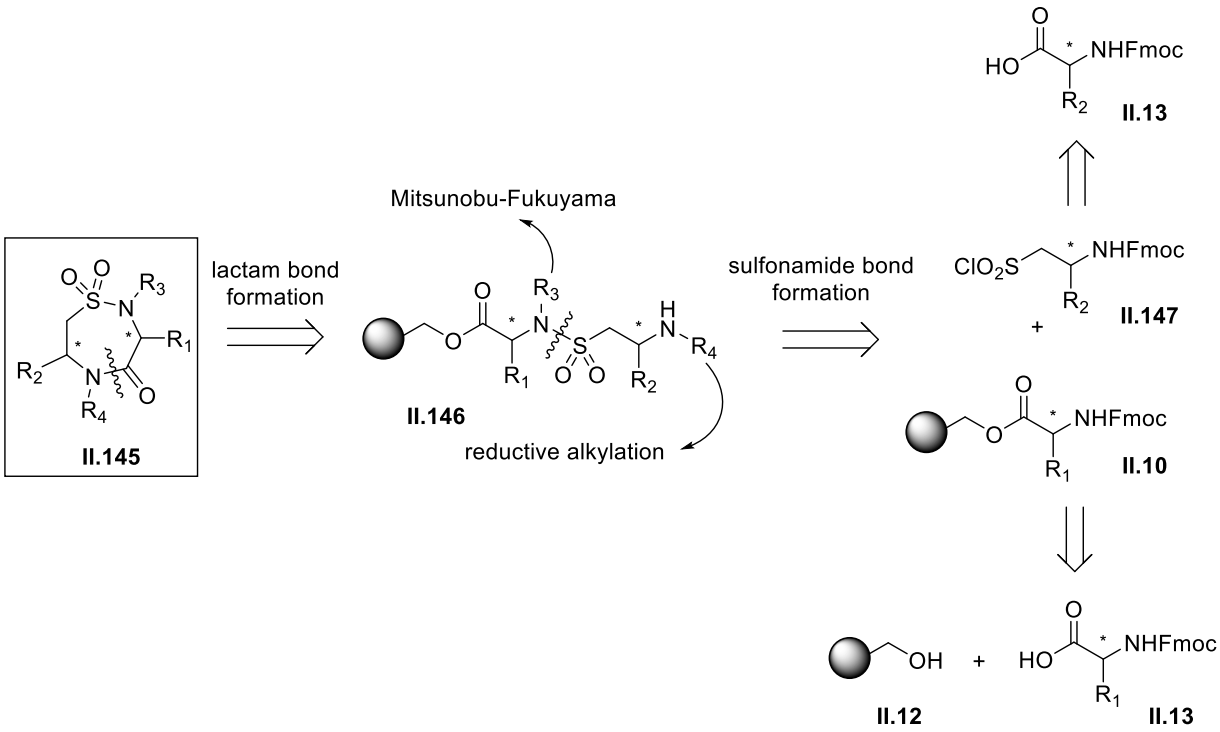
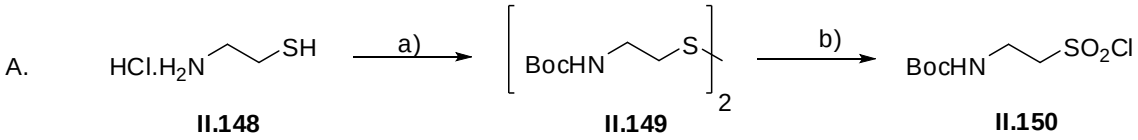


Figure II.48 *Retrosynthetic overview of the approach towards 1,2,5-thiadiazepan-4-one-1,1-dioxides* ***II.145***

The 1,2,5-thiadiazepan-4(5*H*)-one-1,1-dioxides **II.145** are structurally quite similar to their benzofused counterparts and can therefore be synthesized in an almost identical fashion (*figure* ***II.48***). The final step consists, as with the benzothiadiazepinones, of the ring closure and concomitant cleavage by formation of a lactam bond. The N_2 and N_5-positions can be diversified respectively by using a Mitsunobu-Fukuyama alkylation and a reductive alkylation. Subsequently, the sulfonamide bond can be disconnected, resulting in a β-aminoethanesulfonyl chloride building block **II.147** and a solid supported α-amino acid **II.10**. The first can be synthesized starting from Fmoc protected α-amino acids **II.13**, the latter by a simple coupling of an α-amino acid **II.13** to a suitable solid support **II.12**.

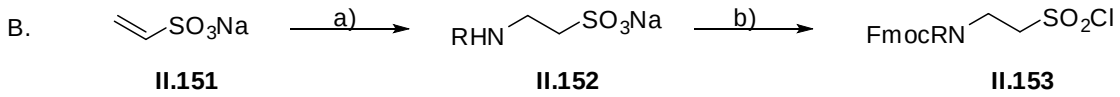
3.1.2 β-AMINOETHANESULFONYL CHLORIDES

To synthesize the seven membered thiadiazepanones **II.145**, β-aminoethanesulfonyl chlorides **II.147** are essential building blocks. Thanks to their versatility[232], several syntheses towards these building blocks have already been described in the literature[233]. Two examples of those synthetic strategies are briefly outlined in figure **II.49**, followed by the general synthesis applied during this research in figure **II.50**. In the first case, the β-aminoethanesulfonyl chloride **II.150** was synthesized starting from the hydrochloric acid salt of 2-aminoethanethiol, which was oxidized and protected towards the disulfide **II.149**. Subsequent oxidative chlorination using chlorine and acetic anhydride readily delivered the desired sulfonyl chloride **II.150** (*figure **II.49-A***). A second strategy[234] commenced with the Michael addition of an amine to a vinylsulfonate **II.151**, resulting in compound **II.152**. After protecting the amine with a Fmoc-group and chlorination of the sulfonate using phosgene[235], the desired sulfonyl chloride **II.153** was obtained (*figure **II.49-B***).



II.148 **II.149** **II.150**

a) i. I_2, NaOH, dioxane/H_2O ii. Boc_2O b) 5 eq. Cl_2, 4 eq. Ac_2O



II.151 **II.152** **II.153**

a) R-NH_2, H_2O b) i. FmocCl, dioxane/H_2O ii. $COCl_2$ in toluene (20% v/v), DMF, CH_2Cl_2

Figure II.49-A & B *Two synthetic pathways towards β-aminoethanesulfonyl chlorides*

The strategy applied during this research was optimized by Liskamp *et al.* and started from suitably protected α-amino acids, because this allowed to obtain the broadest diversity of β-aminoethanesulfonyl chlorides[236] (*figure **II.50***). First, the Fmoc-protected α-amino acids **II.13** were

[232] β-aminoethanesulfonyl chlorides have been used in the synthesis of compounds with different applications such as receptor molecules, catalysts and peptidomimetics: a) Gennari, C.; Nestler, P. H.; Salom, B.; Still, C. W. *Angew. Chem. Int. Ed.* **1995**, *34(16)*, 1765-1768. b) Löwik, W. P. M. D.; Weingarten, M. D.; Broekema, M.; Brouwer, A. J.; Still, C. W.; Liskamp, R. M. J. *Angew. Chem. Int. Ed.* **1998**, *37*, 1846-1850. c) Gennari, C.; Ceccarelli, S.; Piarulli, U.; Montalbetti, C. A. G. N.; Jackson, R. F. W. *J. Org. Chem.* **1998**, *63(16)*, 5312-5313.

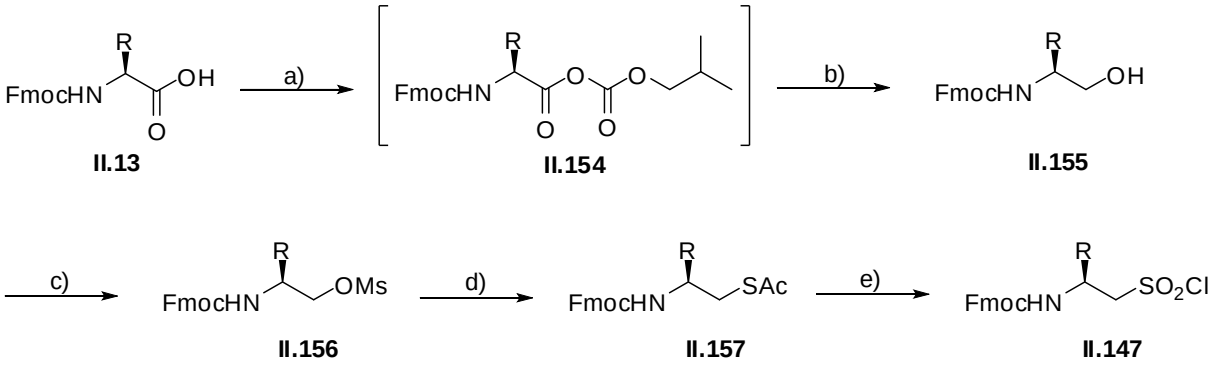
[233] a) Moree, W. J.; van der Marel, G. A.; Liskamp, R. M. J. *J. Org. Chem.* **1995**, *60(16)*, 5157-5169. b) Lowik, D. W. P. M.; Liskamp, R. M. J. *Eur. J. Org. Chem.* **2000**, *2000(7)*, 1219-1228. c) Higashiura, H.; Morino, H.; Matsuura, H.; Toyomaki, Y.; Ienaga, K. *J. Chem. Soc. Perkin Trans I* **1989**, *1989(8)*, 1479-1481. d) Gude, M.; Piarulli, U.; Potenza, D.; Gennari, C. *Chem. Eur. J.* **1998**, *4(10)*, 1924-1931. e) Gude, M.; Piarulli, U.; Potenza, D.; Salom, B.; Gennari, C. *Tetrahedron Lett.* **1996**, *37(47)*, 8589-8592.

[234] van Ameijde, J.; Liskamp, R. M. J. *Tetrahedron Lett.* **2000**, *41(7)*, 1103-1106.

[235] In some cases phosgene is replaced by SO_2Cl or triphosgene: a) Carson, K.G.; Schwender, C. F.; Schroff, H. N.; Cochran, N. A.; Gallant, D. L.; Briskin, M. J. *Bioorg. Med. Chem. Lett.* **1997**, *7(6)*, 711-714. b) Gude, M.; Piarulli, U.; Potenza, D.; Salom, B.; Gennari, C. *Tetrahedron Lett.* **1996**, *37(47)*, 8589-8592.

[236] Brouwer, A. J.; Monnee, M. C. F.; Liskamp, R. M. J. *Synthesis* **2000**, *2000 (11)*, 1579-1584.

reduced to the corresponding aminoalcohols **II.155** in a two-step sequence[237]: formation of the reactive intermediate **II.154** by reacting isobutyl chloroformate and the α-amino acid, immediately followed by a reduction using $NaBH_4$. This procedure afforded the aminoalcohols **II.155** in a fast and clean way, with no loss of optical activity.



a) iBuOCOCl, NMM, DME, -10°C, 1 min b) $NaBH_4$, H_2O, -10°C, 1 min c) MsCl, Et_3N, CH_2Cl_2, 0°C, 2 h d) HSAc, Cs_2CO_3, DMF, RT, 16 h e) i. H_2O_2, HOAc, RT, 16 h ii. $COCl_2$ (20% v/v in toluene), DMF, CH_2Cl_2, RT, 2 h

Figure II.50 *Synthesis of diverse β-aminoethanesulfonyl chlorides*

To obtain the thioacetates **II.157**, the first pathway that was considered by the authors was the direct formation of the thioacetate using a Mitsunobu reaction. Unfortunately, a side reaction with formation of the Michael adduct of thioacetate and DIAD took place under these reaction conditions. Also, the purification of the thioacetate **II.157** appeared to be quite difficult, leading to non-reproducible results. As a result, a two-step procedure was devised in which the alcohols were first transformed to their corresponding mesylates **II.156** using methanesulfonyl chloride in the presence of triethylamine. Now, a nucleophilic substitution reaction could be performed by adding the mesylates to a mixture of thioacetic acid and cesium carbonate in DMF. A slight excess of cesium carbonate was needed for a total conversion of the starting material, but caution had to be exercised when using this base to avoid cleavage of the Fmoc-protecting group. The following step consisted of the oxidation of the thioacetates **II.157** to the corresponding sodium sulfonate. This reaction was performed in a mixture of acetic acid and hydrogen peroxide, forming peracetic acid *in situ*, which readily oxidized the thioacetates to the sulfonates. The reaction was worked up by stirring the sulfonate in the presence of an excess of sodium acetate, leading to the sodium sulfonate salts. These crude sodium salts were then chlorinated to form the desired β-aminoethanesulfonyl chlorides **II.147** by stirring them in a solution of phosgene in toluene and dichloromethane, together with a catalytic amount of DMF. Initially, the authors tried to chlorinate the sodium salts with triphosgene, a safer alternative for the use of phosgene, but they experienced problems during the purification. As a consequence, residual triphosgene seemed to form isocyanates when used for the peptide couplings, leading to urea byproducts. Phosgene however could be easily removed during workup by evaporation and was

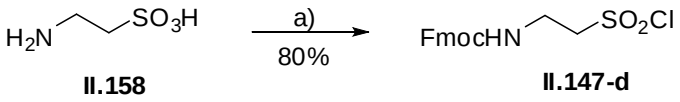
[237] Rodriguez, M.; Llinares, M.; Doulut, S.; Heitz, A.; Martinez, J. *Tetrahedron Lett.* **1991**, *32(7)*, 923-926.

therefore chosen as the preferred chlorinating agent. The obtained β-aminoethanesulfonyl chlorides **II.147** are depicted in *table **II.24***.

PRODUCT	R	II.155	II.156	II.157	II.147	Overall
a	Me	94%	80%	62%	71%	33%
b	Bn	96%	86%	56%	81%	37%
c	CH_2OtBu	75%	99%	77%	67%	38%

Table II.24 *Overview of the yields of each compound during β-aminoethanesulfonyl chloride **II.147** synthesis (yields all measured after purification)*

Fmoc–β-Aminoethanesulfonyl chloride **II.147-d** could be derived from the natural product taurine (**II.158**). Fmoc-protection was performed using Fmoc chloride in a mixture of water and acetonitrile. The pH of the reaction had to be kept between 8 and 9, to avoid amine protonation or premature Fmoc cleavage. Subsequently, the sulfonate was chlorinated as with the other building blocks, using a solution of phosgene in toluene (*figure **II.51***).



II.158 **II.147-d**

a) i. Fmoc-Cl, H_2O, pH 8-9, CH_3CN ii. $COCl_2$ (20% v/v in toluene), DMF, CH_2Cl_2, rt

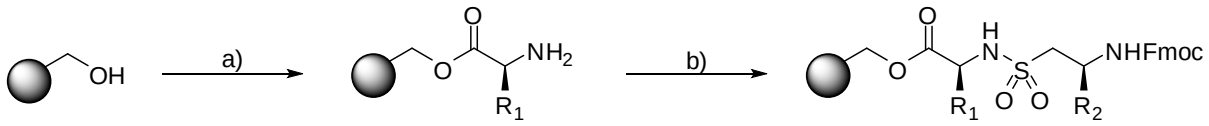
Figure II.51 *Synthesis of β-aminoethanesulfonyl chloride **II.147-d***

3.1.3 SYNTHESIS OF THE 1,2,5-THIADIAZEPAN-4-ONE-1,1-DIOXIDES

3.1.3.1 COUPLING OF THE α-AMINO ACIDS AND β-AMINOETHANESULFONYL CHLORIDES

As in the case of the benzothiadiazepinones, the first step consisted of the coupling of an α-amino acid onto Wang resin **II.23** using the DIC/DMAP protocol (*figure **II.52***). After deprotection of the Fmoc group, the β-aminoethanesulfonyl chloride building blocks **II.147** could be readily attached. A first test reacting the resin 16 h with 6 equivalents of building block in the presence of 10 equivalents of *sym*-collidine[238] was not sufficient for a complete conversion of the amine towards the sulfonamide. Repeating this reaction a second time under the same conditions, finally delivered the desired product **II.159**. However, this was at the expense of 12 equivalents of our building block **II.147**, which was certainly not efficient enough. It was considered then that a nucleophilic catalyst such as DMAP, could probably improve this reaction. Indeed, shaking the resin for 16 h in the presence of 3 equivalents of β-aminoethanesulfonyl chloride **II.147**, 6 equivalents of *sym*-collidine and 0,1 equivalents of DMAP yielded the sulfonamide **II.159**.

[238] Monnee, M. C. F.; Marijne, M. F.; Brouwer, A. J.; Liskamp, R. M. J. *Tetrahedron Lett.* **2000**, *41(41)*, 7991-7995



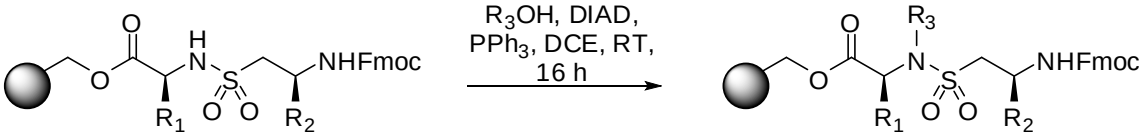
II.23 **II.24** **II.159**

a) i. Fmoc-L-AA-OH, DIC, DMAP, CH_2Cl_2, RT, 16 + 3 h ii. 20% 4-Me-piperidine in DMF, RT, 2x 10 min
b) **II.147-(a-d)**, *sym*-collidine, DMAP, CH_2Cl_2, RT, 16 h

Figure II.52 *α-Amino acid coupling, Fmoc deprotection and coupling of a β-aminoethanesulfonyl chloride* ***II.147-(a-d)***

3.1.3.2 MITSUNOBU-FUKUYAMA ALKYLATION OF N_2 AND FMOC DEPROTECTION

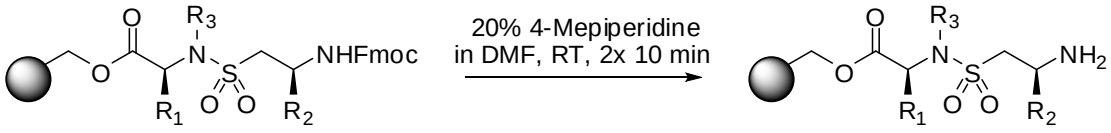
With the sulfonamide in hands, the N_2 position could readily be alkylated. The pK_a of the sulfonamide, around 11-12, should normally be sufficient to allow a Mitsunobu-Fukuyama reaction. However, this rather high pK_a value will probably cause the reaction to be slower compared to the common protocol which makes use of the electron deficient nosyl group. Therefore, we decided to shake the resin **II.159** for 16 h in the presence of 10 equivalents of methanol, 5 equivalents of diisopropylazodicarboxylate and 5 equivalents of triphenylphosphine (*figure* ***II.53***). In this way, a complete conversion was accomplished for this substrate, delivering the N-alkylated product **II.160**.



II.159 **II.160**

Figure II.53 *Mitsunobu-Fukuyama alkylation of sulfonamide* ***II.159***

Before we could perform the cyclization/release reaction, the amine had to be deprotected (*figure* ***II.54***). This Fmoc deprotection reaction however posed a threat, because the basic 4-methylpiperidine could be sufficient to induce a premature ring closure. Therefore, a small amount of the resin **II.160** was reacted for 4 h in the presence of a 20% solution of 4-methylpiperidine in DMF after which the filtrate was analyzed for traces of a ring closed product. Fortunately, no product was found in the filtrate, making these reaction conditions suitable for further use.



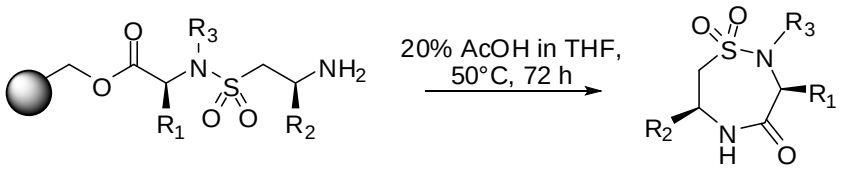
II.160 **II.161**

Figure II.54 *Fmoc deprotection of compound* ***II.160***

3.1.3.3 RING CLOSURE OF NON-N_5-ALKYLATED RING CLOSING PRECURSOR ***II.161***

After Fmoc deprotection, the released amine **II.161** was ready to undergo the cyclization reaction. Three conditions were tested for this ring closure, based on literature precedents for similar substrates: (1) using 5 equivalents of acetic acid in dichloromethane, (2) using 2,2 equivalents of N,N-

diisopropylethylamine together with 5 equivalents of acetic acid in dichloromethane and (3) using 5 equivalents of 2-pyridone in dichloromethane. Each of those methods delivered the desired product, but due to the ease of workup, the use of 5 equivalents of acetic acid was chosen as the preferred cyclization/release protocol. However, the yields of the products after 16h stirring at room temperature where very low (<4%), so this protocol still needed to be optimized. After performing some tests at different temperatures and with different solvents, the optimized conditions were found: 72h of stirring at 50°C in a 20% solution of AcOH in THF afforded the desired compounds, while no ring closing precursor was left on the solid support, indicating that the point of full conversion of the starting material was reached (*figure* ***II.55***). These conditions were further applied for the cyclization/release reaction of a small library of 1,2,5-thiadiazepan-4-one-1,1-dioxides diversified at three positions (*table* ***II.25***).



II.161 **II.145**

Figure II.55 *Optimized conditions for the cyclization/release reaction towards the 1,2,5-thiadiazepan-4-one-1,1-dioxides* ***II.145***

PRODUCT	R_1	R_2	R_3	YIELD[a]
a	H	H	Me	50%
b	Bn	H	Me	44%
c	(N-Trt)-imidazol-4-ylmethyl	H	Me	41%
d	(N-Boc)-indol-3-ylmethyl	H	Me	16%
e	H	CH_2OtBu	Me	49%
f	Bn	CH_2OtBu	Me	42%
g	(N-Boc)-indol-3-ylmethyl	CH_2OtBu	Me	20%
h	H	Bn	Me	92%
i	H	Bn	Bn	47%
j	iBu	Bn	Me	48%
k	Bn	Me	4-fenylbenzyl	17%
l	iBu	Me	Me	70%
m	Bn	Me	Me	60%
n	$(CH_2)_2COO(tBu)$	Me	Me	68%
o	H	Me	Me	48%
p	iBu	Bn	Bn	77%

[a] Yields are measured after purification and based upon the initial resin loading

Table II.25 *Overview of the synthesized 1,2,5-thiadiazepan-4-one-1,1-dioxides* ***II.145*** *diversified on three positions*

Because of the mild acidic reaction conditions, no epimerization was expected for these structures. Indeed, nor in the LC-MS chromatogram nor in the NMR spectra of the cyclized products a trace of a possible diastereomer was detected.

3.1.3.4 N_5-ALKYLATION

As in the case of the benzothiadiazepinones, the released N_5-amine moiety could already be alkylated on resin (*figure **II.56***). Because this now consisted of an aliphatic primary amine, the danger of overalkylation was present and probably unavoidable when using a reductive amination. Indeed, applying the previous conditions used for reductive aminations on compound **II.161**, the dibenzylated product **II.163** was formed before full conversion towards the mono-benzylated product **II.162**.

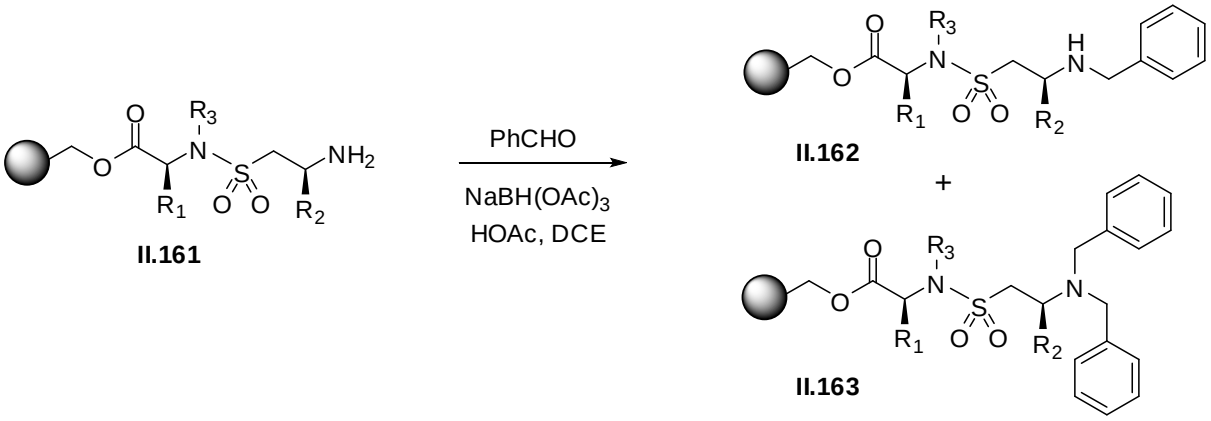
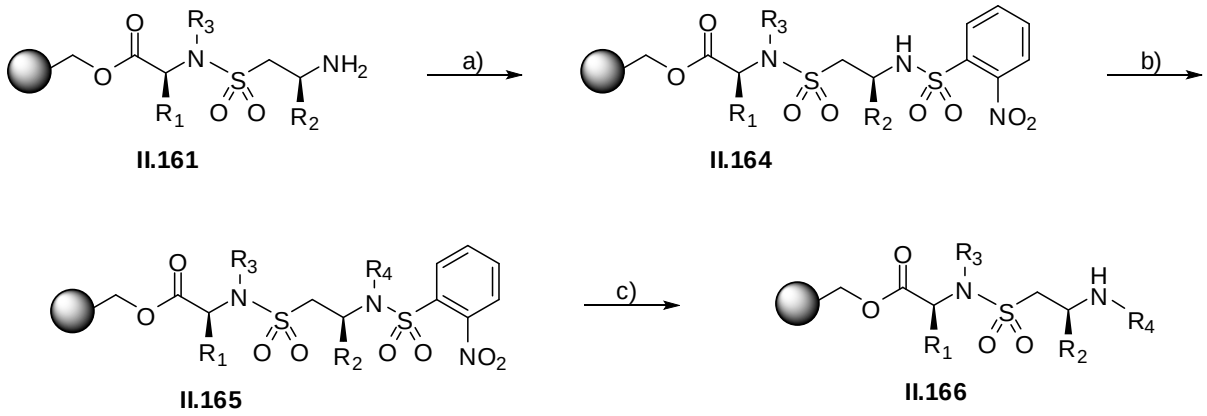


Figure II.56 *Overalkylation of the N_5-position when applying a reductive amination*

We then decided to replace the reductive amination reaction by a second Mitsunobu-Fukuyama reaction (*figure **II.57***). Although this requires an extra protection and deprotection step, this strategy cannot lead to overalkylation. First, *ortho*-nosylchloride was coupled to the primary amine **II.161** in the presence of *sym*-collidine in dichloromethane and readily yielded compound **II.164**. The sulfonamide could then readily be alkylated using the previously applied Mitsunobu conditions: 10 equivalents of an alcohol, 5 equivalents of diisopropylazodicarboxylate and triphenylphosphine in DCE. However, to reach complete conversion, the reaction had to be repeated three times. After the successful alkylation towards **II.165**, the *ortho*-nosyl group had to be removed again. As mentioned before, the *ortho*-nosyl group is cleaved in the presence of strong nucleophiles such as thiolates. A literature example for a deprotection on solid phase [239] describes the use of a 0.5 M solution of β-mercaptoethanol in DMF together with 5 equivalents of DBU. These conditions were slightly adapted by us, shaking the resin for 2x 30 min in the presence of 2.5 equivalents of β-mercaptoethanol and 5 equivalents of DBU. This led to a complete cleavage of the nosyl group, delivering the ring closing precursor **II.166**.

[239] Wels, B.; Kruijtzer, J. A. W.; Liskamp, R. M. J. *Org. Lett.* **2002**, *4(13)*, 2173-2176



a) *o*-NsCl, *sym*-collidine, CH_2Cl_2, RT, 2x 1 h b) R_4-OH, DIAD, PPh_3, DCE, RT, 3x 2 h c) β-mercaptoethanol, DBU, DMF, RT, 2x 30 min

Figure II.57 *Alkylation of the N_5-amine using a Mitsunobu-Fukuyama protocol*

*3.1.3.5 RING CLOSURE OF N_5-ALKYLATED RING CLOSING PRECURSOR **II.166***

The problems that raised during the ring closure of the N_5-alkylated benzothiadiazepinones, were also not unthinkable for the N_5-alkylated thiadiazepanones **II.145**. The sterical hindrance during ring closing compounds **II.166** was comparable to that encountered for the benzothiadiazepines. However, it was also feared that the flexibility of the β-aminoethane chain would slow up the ring closure. However, when applying the same ring closing conditions as for the non-N_5-alkylated thiadiazepanones, we readily obtained the desired N_5-alkylated thiadiazepanes **II.145** (*figure **II.58***).

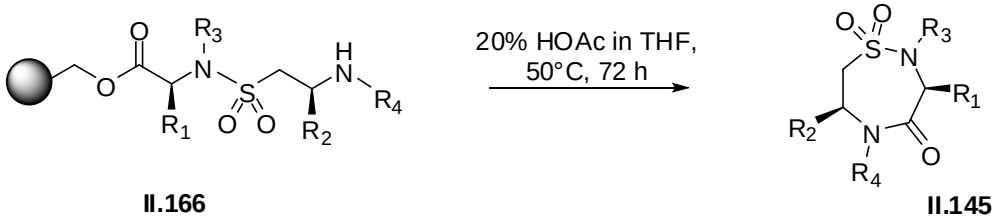
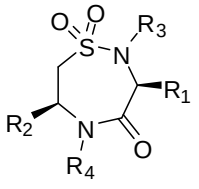


Figure II.58 *The cyclization/release reaction towards the 5-alkyl-1,2,5-thiadiazepin-4-one-1,1-dioxides **II.145***

These conditions were applied for the synthesis of a small library, depicted in *table **II.26***. The yields of these products were significantly lower as compared to those of the non-N_5-alkylated products, due to the fact that the ring closing conditions were not yet optimized for these compounds. Indeed, a test reaction of the ring closure using a 50% acetic acid solution in THF shaking for 120 h at 50°C, revealed that there was still some unreacted ring closing precursor left on the solid support. Increased temperatures or the use of a nucleophilic catalyst could probably improve the yields.



II.145

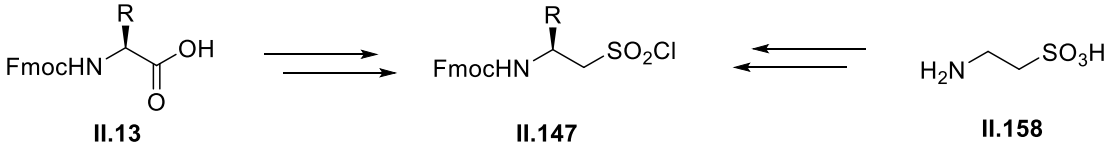
PRODUCT	R_1	R_2	R_3	R_4	YIELD
q	$(CH_2)_2COO(tBu)$	H	Me	Me	38%
r	H	H	Me	Me	22%
s	iBu	H	Me	4-fenylbenzyl	9%
t	iBu	H	Me	2-(N-morpholino)-Et	18%
u	Bn	H	Me	Me	30%
v	H	Bn	Me	Me	41%
w	Bn	H	Me	4-fenylbenzyl	12%
x	H	Bn	Me	Bn	10%
y	iBu	Bn	Me	Me	3%

[a] Yields are measured after purification and based upon the initial resin loading

Table II.26 *Overview of the synthesized 1,2,5-thiadiazepan-4-one-1,1-dioxides* ***II.145*** *diversified at four positions*

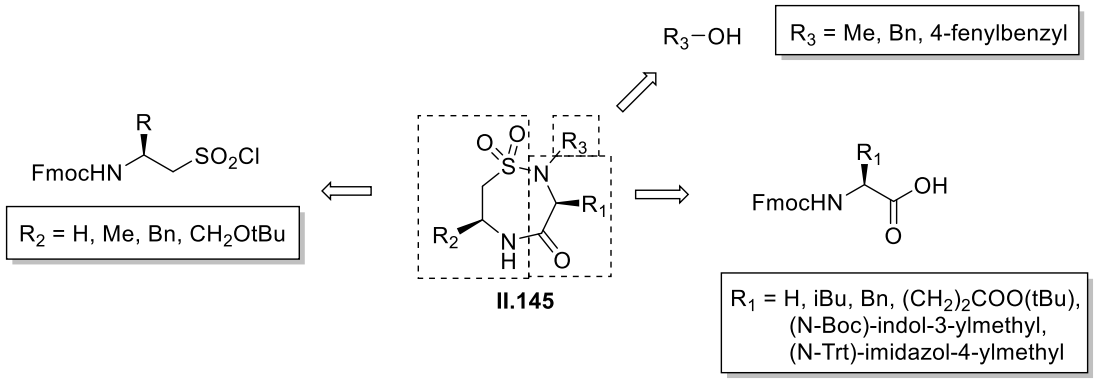
3.2 CONCLUSION

In this second part, the solid phase synthesis towards 1,2,5-thiadiazepan-4-one-1,1-dioxides **II.145** was investigated. The proposed synthetic method to obtain these target compounds consisted of a cyclization/release strategy, similar to the one applied during the synthesis of the benzothiadiazepinones. Essential, but commercially unavailable building blocks for this synthetic route were β-aminoethanesulfonyl chlorides **II.147**. These building blocks were readily accessible starting from commercially available Fmoc-protected α-amino acids in four steps via a literature procedure. In this way, three β-aminoethanesulfonyl chlorides **II.147-(a-c)** were obtained in good yields. β-Aminoethanesulfonyl chloride **II.7-d** could be obtained in a two-step procedure starting from commercially available taurine, adding a fourth building block to our list.



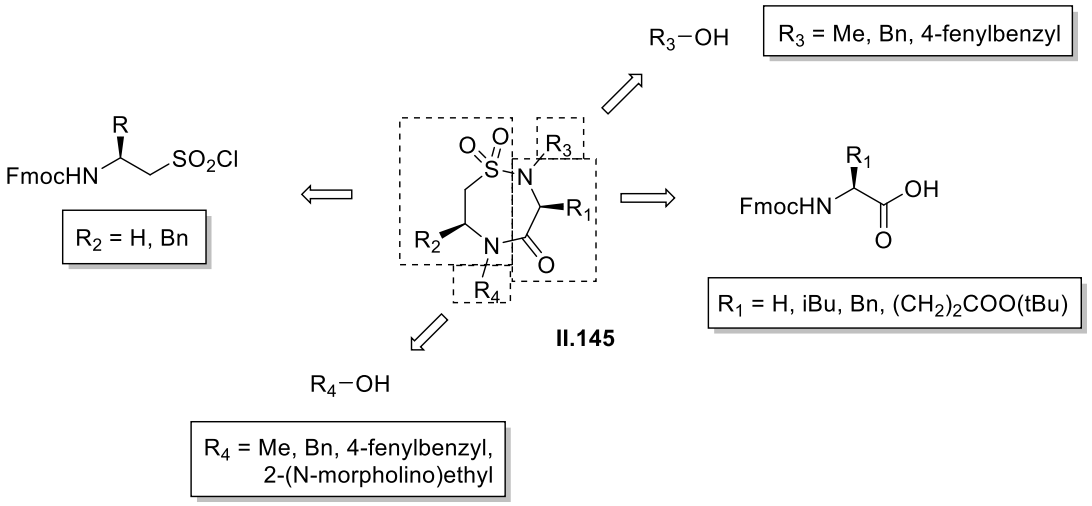
II.147-a (R = Me): 33%
II.147-b (R = Bn): 37%
II.147-c (R = CH_2OtBu): 38%
II.147-d (R=H): 80%

The solid phase synthesis of these thiadiazepanones went smoothly applying the proposed synthetic route. This led to ring closing precursor **II.161**, which was diversified at 3 positions using different α-amino acids, β-aminoethanesulfonyl chlorides and alcohols. The cyclization/release reaction could be induced with a mild acid, in this case by using a solution of 20% acetic acid in THF at 50°C for 72 h. A small library of seventeen 1,2,5-thiadiazepan-4-one-1,1-dioxides **II.145-(a-p)** was obtained in this way in good to excellent yields (16-92%). By avoiding strongly basic or acidic conditions, the resulting 1,2,5-thiadiazepan-4-one-1,1-dioxides **II.145** were also enantiomerically pure.



A fourth substituent could be introduced at the N_5-position using the Mitsunobu-Fukuyama protocol. This 3-step method was needed because a direct reductive amination of the primary amine led to overalkylation. Although problems were anticipated during the cyclization reaction of precursor **II.166**, the ring closure went using the same conditions as for the non-N_5-alkylated products. Nine N_5-alkylated 1,2,5-thiadiazepan-4-one-1,1-dioxides **II.145-(q-y)** could be obtained in this way in satisfying yields.

These conditions were however not yet optimal, as suggested by the fact that there was still ring closing precursor present on the solid support after the final ring closure. Optimization of the cyclization/release reaction conditions is therefore still needed.



4 SYNTHESIS OF 3,4-DIHYDRO-2*H*-1,2,6-BENZOTHIADIAZOCIN-5(6*H*)-ONE-1,1-DIOXIDES

The last scaffold that was tackled during this project consisted of the 8-membered 3,4-dihydro-2*H*-1,2,6-benzothiadiazocin-5(6*H*)-one-1,1-dioxides **II.167**, and more specifically the analogs in which an alicyclic ring is annulated via the positions 3 and 4. The choice for these scaffolds was based on the fact that they were yet unexplored, despite a good pharmaceutical profile and a particular structural conformation (*vide infra*).

4.1 ON-RESIN CYCLIZATION

4.1.1 RETROSYNTHETIC OVERVIEW

The synthesis strategy of choice for these 8-membered rings is the on-resin cyclization, because of its superior ring closing properties compared to the cyclization/release strategy. This will certainly be needed, because 8-membered lactams are even more difficult to form than their 7-membered analogs[240]. The build-up of these molecules is nearly identical as in the case of the benzothiadiazepines. The difference lies in the type of amino acid, which now consists of an alicyclic β-amino acid **II.170** instead of an α-amino acid (*figure **II.59***). The Fm-esters of the alicyclic β-amino acids **II.170** are not commercially available and thus synthesized in our lab starting from cyclic alkenes **II.171**.

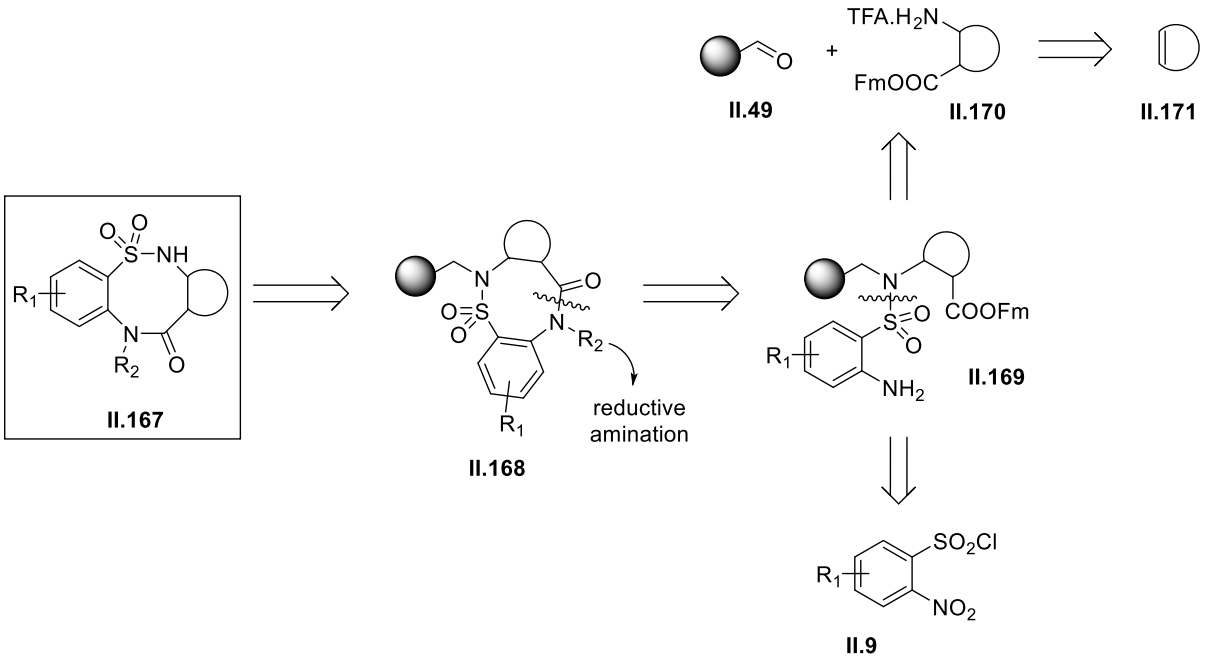
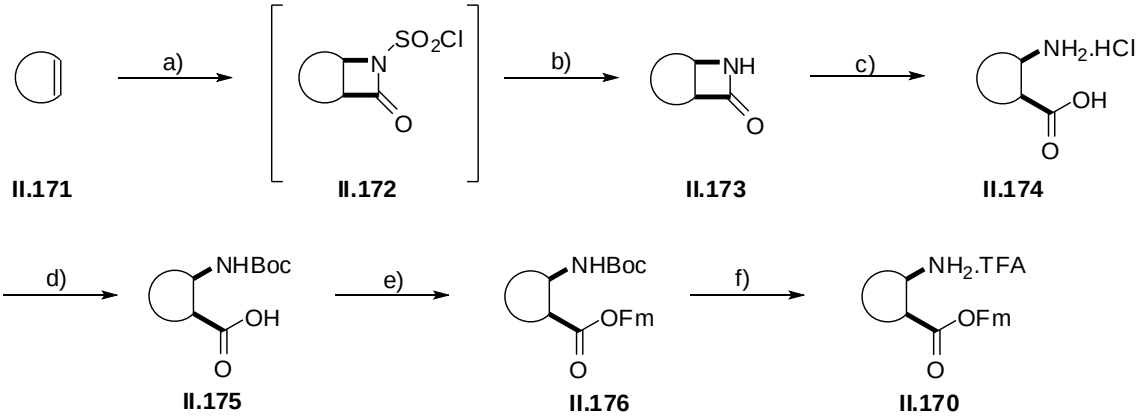


Figure II.59 *Retrosynthetic overview of the on-resin cyclization synthesis of the 3,4-dihydro-2H-1,2,6-benzothiadiazocin-5(6H)-one-1,1-dioxides*

[240] Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14(4)*, 95-102

4.1.2 FLUORENYLMETHYL PROTECTED ALICYCLIC β-AMINO ACIDS **II.170**

The synthesis of eight membered benzodiazocinones requires suitably protected β-amino acids for their buildup using the on-resin cyclization strategy. For the same reasons as the previous building blocks, our choice fell on the fluorenylmethyl protective group. Also, the procedure to synthesize the racemic fluorenylmethyl protected alicyclic *cis*-β-amino acids was already optimized in our lab and could therefore be readily applied (*figure **II.60***). The synthesis starts from a commercially available cycloalkene **II.171**, which is reacted with chlorosulfonyl isocyanate (CSI) and delivers the N-chlorosulfonyl *cis*-β-lactam **II.172**[241]. This intermediate is not isolated but directly reduced to the corresponding *cis*-β-lactam **II.173** in the presence of $NaHSO_3$ and NaI[242]. In the next step, the cyclic *cis*-β-amino acid **II.174** is delivered by opening the β-lactam in concentrated hydrogen chloride. Before the fluorenylmethyl group could be introduced on the carboxyl, the amine is first protected as a *tert*-butyl carbamate using di-*tert*-butyldicarbonate in the presence of potassium carbonate. To avoid racemization at the α-position of the carboxyl group, it is extremely important that only 1 equivalent of base is added during this reaction. Fluorenylmethyl protection of the carboxylic acid using DCC/DMAP in dichloromethane, subsequently followed by Boc-deprotection in a 25% solution of TFA in dichloromethane readily yielded the desired *cis*-β-amino acid salts **II.170**. The yield for each synthetic step is summarized in *table **II.27***.



a) i. CSI, CH_2Cl_2, 0°C, 1 h ii. RT, 16h - 48h b) NaI, $NaHSO_3$, H_2O, RT c) 12M HCl, 90°C, 1 h d) Boc_2O, K_2CO_3, dioxane/water 2/1, RT, 16 h e) FmOH, DCC, DMAP, CH_2Cl_2, 0°C, 6 h f) 25% TFA in CH_2Cl_2, RT, 1 h

Figure II.60** The synthesis of alicyclic cis-β-Amino acids **II.170

PRODUCT	II.171	II.173	II.174	II.175	II.176	II.170	Overall
a	cyclopentene	72%	64%	84%	79%	89%	27%
b	cyclohexene	55%	93%	71%	87%	92%	29%

***Table II.27** Overview of the yields of each reaction during alicyclic β-amino acid synthesis*

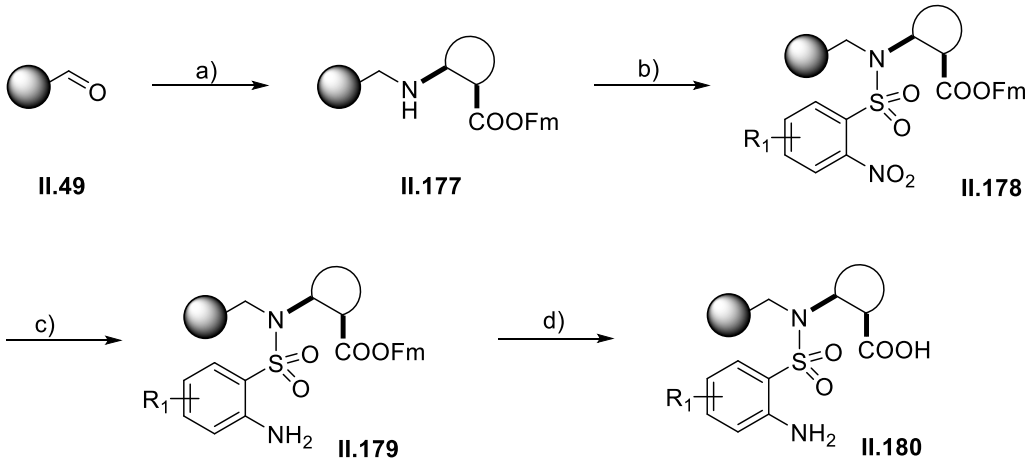
[241] a) Moriconi, E. J.; Crawford, W. C. *J. Org. Chem.* **1968**, *33(1)*, 370-378 b) Dener, J. M.; Fantauzzi, P. P.; Kshirsagar, T. A.; Kelly, D. E.; Wolfe, A. B. *Org. Proc. Res. Dev.* **2001**, *5(4)*, 445-449

[242] Graf, R. *Liebigs Ann. Chem.* **1963**, *661(1)*, 111-157

4.1.3 3,4-DIHYDRO-2*H*-1,2,6-BENZOTHIADIAZOCIN-5(6*H*)-ONE-1,1-DIOXIDES

*4.1.3.1 SYNTHESIS TOWARD RING CLOSING PRECURSOR **II.180***

As in the other cases where the on-resin cyclization strategy was applied, the choice of solid support fell again on the reliable FMPB-resin (*figure **II.61***). The coupling of the β-amino acids on the resin was conducted in the same fashion as the α-amino acid coupling was done, by adding 4,5 equivalents of sodium triacetoxyborohydride to the resin and shaking it overnight. This delivered the desired coupled amino acids **II.177** in almost quantitative yields. Subsequently, a nosyl type building block **II.9** was coupled according to the analogous coupling during the benzothiadiazepinone synthesis. After shaking 2x 1 h in the presence of 5 equivalents nosyl chloride **II.9** and 10 equivalents *sym*-collidine, a full conversion towards products **II.178** was achieved. The reduction of the nitro moiety using chromium(II) chloride also went effortlessly and was immediately followed by the deprotection of the fluorenylmethylester, yielding the ring closing precursor **II.179**. After performing the deprotection, the resin was treated 2x 1 h with a 10% solution of acetic acid in CH_2Cl_2 to remove the residual 4-methylpiperidine.



a) i. **II.137**, $NaBH(OAc)_3$, DCE/DMF 9/1, RT, 16 h ii. 10% DIPEA in CH_2Cl_2, RT, 1 h b) **II.9**, *sym*-collidine, CH_2Cl_2, RT, 2x 1 h c) $CrCl_2$, DMF/MeOH 9/1, RT, 2x 1 h d) i. 20% 4-Mepiperidine in DMF, RT, 2x 10 min ii. 10% HOAc in CH_2Cl_2, RT, 2x 1 h

Figure II.61** On-resin cyclization strategy towards ring closing precursor **II.180

4.1.3.2 RING CLOSURE

The ring closure was tested with two different coupling reagents, namely PyBrop **II.86** and COMU **II.181**. PyBrOP had already proven its value during the difficult on-resin cyclization of the benzothiadiazepinones and was therefore an obvious choice. COMU was chosen as a possible replacement for PyBrOP, because of its high coupling efficiencies in difficult amino acid sequences and low racemization rates. COMU is a coupling reagent that was designed by Albericio *et al.* in 2009 as a replacement for the (explosive) benzotriazole based coupling reagents. It is based on the previously developed additive Oxyma **II.182** or ethyl-2-cyano-2-(hydroximino)acetate (*figure **II.62***).

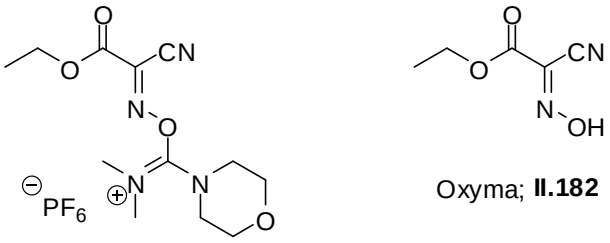
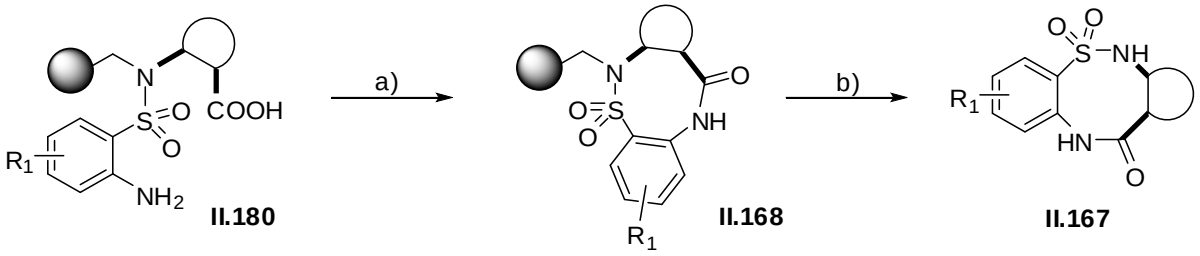


Figure II.62 *Coupling reagents COMU* ***II.147*** *and Oxyma* ***II.148***

The results for COMU were however quite disappointing. After 1 h, only a small amount of ring closed product was found in the LC-chromatogram. Even after 24 h shaking, no full conversion of final products was obtained (<90%). Also, small amounts of byproducts started to form after 24h, making COMU not the ideal coupling reagent for these compounds. With PyBrOP, a smooth conversion towards the ring closed products **II.168** was accomplished in 16 h, making this reagent the one of choice for the on-resin cyclization of the benzothiadiazocinones **II.167**.(*figure* ***II.63***)



a) PyBrOP, DIPEA, DMF, RT, 16 h b) 95% TFA in H_2O, RT, 3 h

Figure II.63 *On-resin cyclization and cleavage of 3,4-dihydro-2H-1,2,6-benzothiadiazocin-5(6H)-one-1,1-dioxides* ***II.167***

In this way, three examples of 3,4-*cis*-fused benzothiadiazocinones were obtained in low yields after cleavage from the solid support (*table* ***II.28***).

PRODUCT	β-AMINO ACID	R_1	YIELD
a	ACPC	H	7%
b	ACHC	H	7%
c	ACHC	Cl	4%

Table II.28 *Overview of the synthesized cis-3,4-annulated 1,2,6-benzothiadiazocin-5(6H)-one-1,1-dioxides ACPC = cis-2-aminocyclopentanecarboxylic acid, ACHC = cis-2-aminocyclohexanecarboxylic acid*

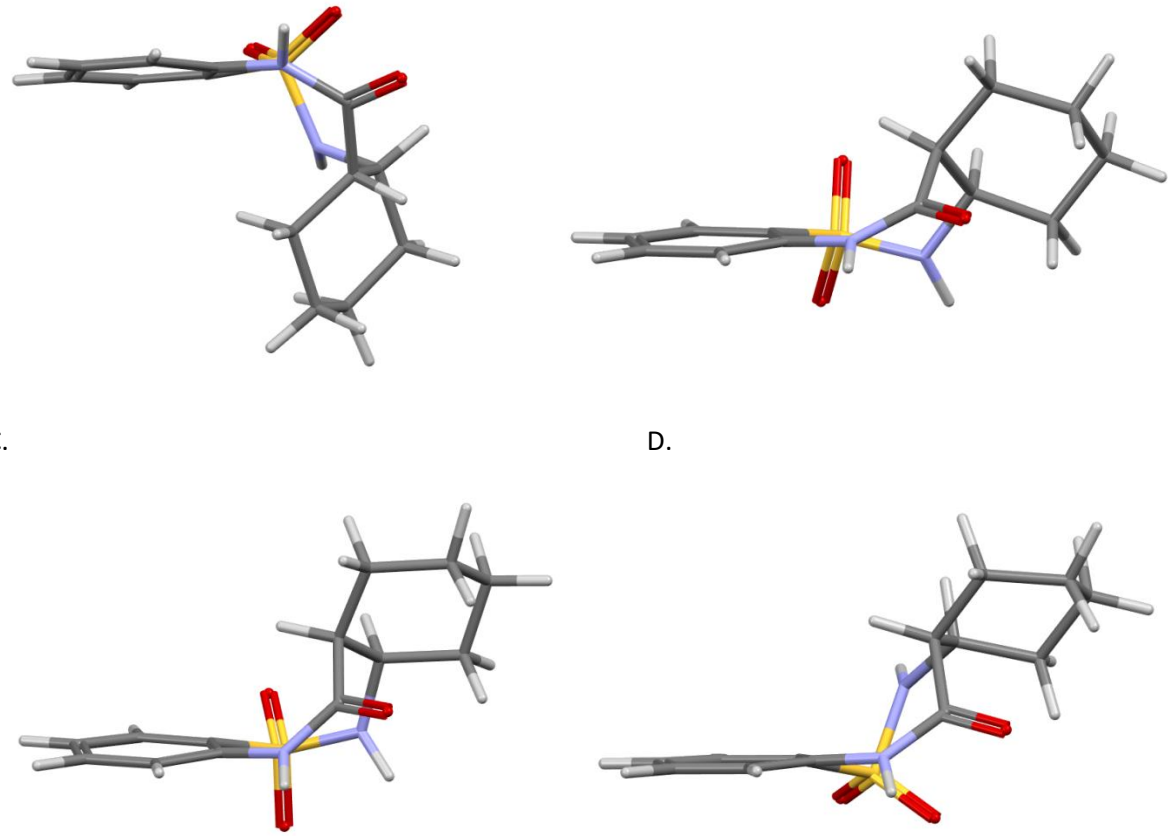
The low yields associated with the on-resin cyclization strategy, both for the seven- and eight-membered systems, suggest that there is a problem related to this method. Previous work in the lab using a similar strategy, describe difficulties with the final cleavage, even in strong acidic conditions. This possibility should therefore be investigated further.

4.2 XRD-ANALYSIS AND MODELLING OF THE SCAFFOLD

4.2.1 MODELING

A modeling study of the 3,4-*cis*-fused tricyclic analog **II.167-b-*cis*** was performed using Maestro software and calculated that the 8-membered ring, adapting a boat-like like conformation, is energetically the most stable structure (*figure **II.64-A***; 0,0 kJ.mol^{-1}). This result is in agreement with the modeled conformation of the structurally related 1,5-benzodiazocin-2,6-diones [243] and 1,6-benzodiazocin-2,5-diones[244], which also adapt this boat-like conformation. Here, the cyclohexane moiety is tilted almost perpendicular compared to the plane of the benzene, while the protons of both the sulfonamide and amide point away from the scaffold.

A. B.



C. D.

Figure II.64 *Modeling results, showing the compounds **II.167-b-cis** with the lowest energy levels **A.** 0,000 kJ.mol^{-1} **B.** 0,679 kJ.mol^{-1} **C.** 2,517 kJ.mol^{-1} **D.** 9,275 kJ.mol^{-1}*

A conformation with a nearly identical potential energy, involves the inversion of the the cyclohexane chair moiety so the H3 switches to psaudo-equatorial position and H4 into a pseudo-axial orientation

[243] Caroen, J. (2012) *Ontwikkeling van een vastefasesynthesestrategie voor 1,2,3,4,5,6-hexahydro-1,5-benzodiazocine-2,6-dionen voor toepassing in combinatorische bibliotheken* Ph.D. Thesis Ghent University: Belgium

[244] Elguero, J.; Fruchier, A.; Llouquet, G.; Marzin, C. *Can. J. Chem.* **1976**, *54(7)*, 1135-1138

(*figure* ***II.64-B***; 0,679 kJ.mol^{-1}). A slightly higher energy level is appointed to the structure with a switched sulfonamide conformation, now pointing the sulfonamide proton pseudo-axially (*figure* ***II.64-C***; 2,517 kJ.mol^{-1}). The final configuration (*figure* ***II.64-D***; 9,275 kJ.mol^{-1}) shows the sulfonamide in a totally different configuration. Other calculated configurations had relative energies higher than 14 kJ.mol^{-1} and were therefore not considered.

4.2.2 XRD-ANALYSIS

Compound **II.167-b** was also crystallized, delivering structural information about this tricyclic system. The space group is Pccn, a centrosymmetric space group, implying that both *cis*-enantiomers are present in the crystal structure. The system adapts a boat-like conformation with the phenylmoeity pointing away from the cyclohexane moiety and with the sulfonamide proton oriented in a pseudo-axial direction (*figure* ***II.65-A***), a configuration matching best with the modeled compound shown in *figure* ***II.64-C***.

A. B.

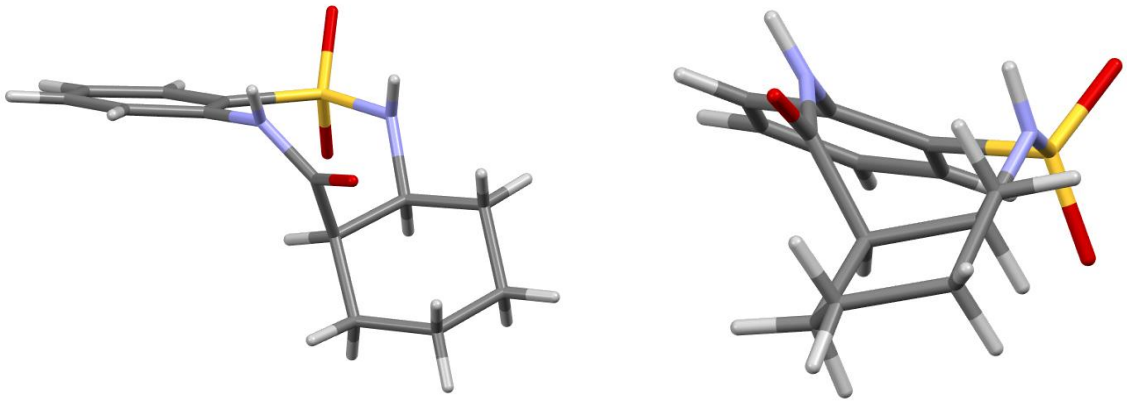
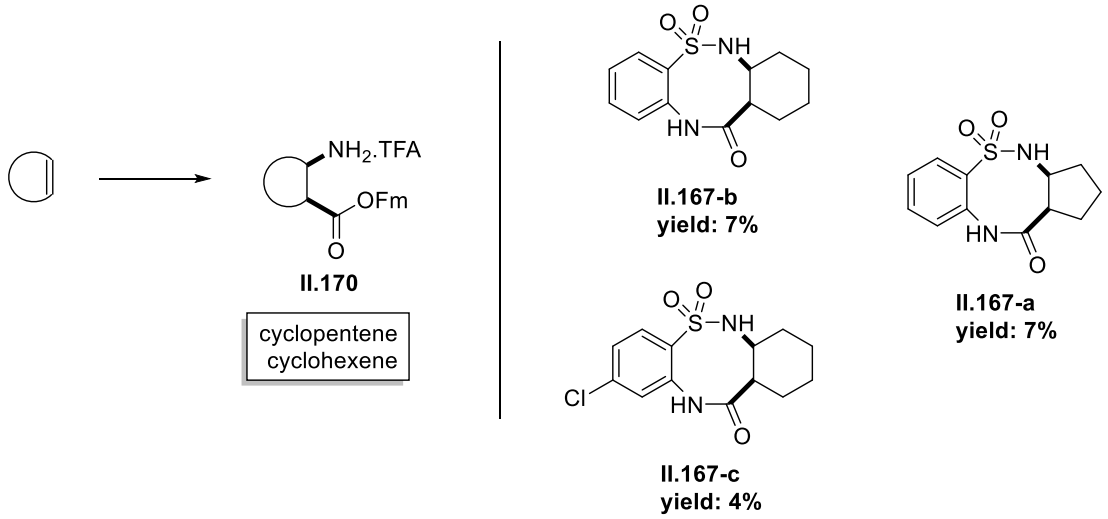


Figure II.65 A & B *Crystal structure of compound* ***II.167-b-cis*** *from different angles*

4.3 CONCLUSION

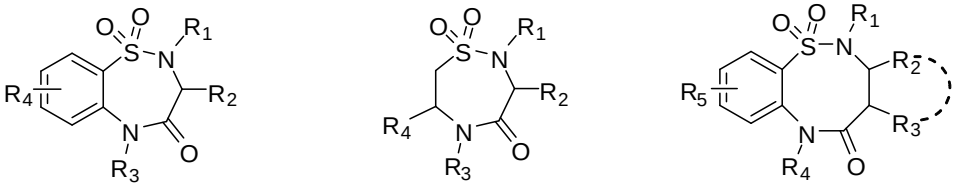
In this part, the solid phase synthesis of the 3,4-dihydro-2*H*-1,2,6-benzothiadiazocin-5(6*H*)-one-1,1-dioxides **II.167** was investigated. Because of the known difficulties considering the ring closure of eight-membered lactams, the on-resin strategy was proposed as the optimal synthetic method towards these scaffolds. The synthetic route ran parallel with the synthesis of the benzothiadiazepinones, except that instead of a Fmoc protected α-amino acid, Fmoc protected alicyclic β-amino acids **II.170** were applied.

These alicyclic β-amino acids could be synthesized according to a procedure that was already established in our lab, starting from cyclopentene and cyclohexene. Applying these β-amino acids in the proposed synthetic route, readily delivered the desired tricyclic compounds **II.167-(a-c)** in low yields. A modeling study of the *cis*-fused thiadiazocine **II.167-b** was performed in our lab and could be matched with the XRD-analysis of this compound.



CHAPTER III: CONCLUSION & FUTURE PERSPECTIVES

The initial goal of this work was the development of a general synthetic route towards three pharmaceutically interesting scaffolds, namely the 2,3-dihydro-1,2,5-benzothiadiazepin-4(5*H*)-one-1,1-dioxides **III.1**, the 1,2,5-thiadiazepan-4-one-1,1-dioxides **III.2** and the 3,4-dihydro-2*H*-1,2,6-benzothiadiazocin-5(6*H*)-one-1,1-dioxides **III.3** (*figure **III.1***). To reach this goal, a solid phase synthetic strategy was developed for each of these scaffolds using commercially available or easily accessible building blocks, allowing a fast and efficient diversification of the target molecules.



III.1 **III.2** **III.3**

Figure III.1 *Target scaffolds*

First, the solid phase synthesis of the 2,3-dihydro-1,2,5-benzothiadiazepin-4(5*H*)-one-1,1-dioxides was tackled. An essential building block in this synthesis consisted of the 2-nitrobenzenesulfonyl chlorides, which had a limited commercial availability. Therefore, a short synthetic route towards these building blocks was developed, starting from commercially available 2-nitrophenols. In this way, eight 2-nitrobenzenesulfonyl chloride building blocks were synthesized. With these building blocks in hand, we were able to synthesize a library of 34 2,3-dihydro-1,2,5-benzothiadiazepin-4(5*H*)-one-1,1-dioxides diversified on three positions using a cyclization/release protocol. The final lactamization with concomitant cleavage, could be induced both by using basic or strongly acidic conditions.

The introduction of a fourth point of diversity on the N_5 position led however to a problematic ring closure. The cyclization/release strategy was abandoned and the alternative on-resin cyclization strategy was tested and optimized towards these target compounds. This method allowed the activation of the carboxylic acid during lactamization, which should improve the ease of ring closure. This BAL-approach ultimately led to the desired N_5 alkylated benzothiadiazepinones, but with the N3 position now serving as anchor point, this strategy also delivered benzothiadiazepinones that could be diversified on only three positions.

Finally, four N_5 alkylated 1,2,5-benzothiadiazepin-4-one-1,1-dioxides were obtained, by building up the target benzothiadiazepinone using the cyclization/release protocol, but by cleaving off the ring closing precursor before lactamization. The ring closure was then performed in solution using the coupling reagent PyBrOP.

Further diversification of this scaffold was accomplished by the on-resin decoration of the benzene moiety, which was made possible by the present functionalities. The 7- and 9-bromosubstituted

compounds were successfully coupled with diverse aryl groups applying an on-resin Suzuki cross coupling reaction, leading to a small library of respectively ten 7-arylated benzothiadiazepinones and three 9-arylated benzothiadiazepinones. The 6- and 8-fluorosubstituted compounds were susceptible for a nucleophilic aromatic substitution reaction, delivering a small library of 6- and 8-aminoalkylbenzothiadiazepinones. And finally, three 7-formylated compounds were transformed to the corresponding 7-alkylaminomethyl substituted analogs.

As a consequence of the use of strong basic and acidic conditions to induce the cyclization/release reaction, the compounds were obtained as their near racemates. Therefore, a synthetic protocol towards the enantiomerically pure compounds was desirable. Both the on-resin cyclization strategy as the conditions used for the ring closure of N_5 alkylated compounds in solution, delivered an enantiopure product.

We can conclude that, despite the problems with the ring closure after N_5 alkylation and racemization of the final products, we managed to optimize a solid phase synthetic route towards 1,2,5-benzothiadiazepin-4-one-1,1-dioxides diversified on at least three positions. This resulted in a library of 71 1,2,5-benzothiadiazepin-4-one-1,1-dioxides in total.

The second target scaffold consisted of the 1,2,5-thiadiazepan-4-one-1,1-dioxides **III.2**. For this type of compound, the non-commercially available β-aminoethanesulfonyl chlorides were necessary building blocks. Applying a synthetic route described by Liskamp *et al.*, we managed to synthesize four of these crucial β-aminoethanesulfonyl chloride building blocks. The cyclization/release strategy that was proposed, delivered no synthetic problems and readily yielded the desired 1,2,5-thiadiazepan-4-one-1,1-dioxides. The final lactam formation was performed successfully in acidic conditions for both the non-N_5 alkylated and N_5 alkylated compounds. In this way, a library of twenty-six 1,2,5-thiadiazepan-4-one-1,1-dioxides diversified on 4 positions was synthesized. No racemization at either one of the stereocentra was detected during synthesis. Future perspectives include the introduction of a diversity point on position 7, by using α-substituted taurine derivatives, and the introduction of functionalized side chains, to extend the substitution possibilities.

The last scaffold that was tackled consisted of the 3,4-dihydro-2*H*-1,2,6-benzothiadiazocin-5(6*H*)-one-1,1-dioxides. It was anticipated that ring closure would be difficult, so the on-resin strategy was chosen as the preferred strategy. After building up the ring closing precursor on-resin according to the proposed synthetic procedure, lactam formation could be induced using PyBrOP as coupling reagent. In this way, three benzothiadiazocines were obtained in low yields after cleavage from the solid support. An X-ray analysis of one of the compounds delivered structural information about the tricyclic system. Before continuing the work on this scaffold, the low yields associated with the on-resin cyclization have to be dealt with. Similar problems were already encountered in our lab using the same strategy and were caused by a difficult cleavage of the final compounds from the solid support. This should therefore be investigated first, before expanding our library.

HOOFDSTUK IV: NEDERLANDSE SAMENVATTING

1 INLEIDING

De recente introductie van gemakkelijk toegankelijke synthetische combinatorische bibliotheken resulteerde in een fundamentele verschuiving in het onderzoek naar nieuwe geneesmiddelen. Daar waar voorheen (tot het midden van de jaren tachtig) geneesmiddelen dienden gezocht te worden in natuurlijke bronnen (planten, dieren, micro-organismen) of bekomen werden na tijdrovende individuele synthese van honderden analogen van actieve basisstructuren, laat de combinatorische benadering tegenwoordig toe om op relatief korte tijd een grote verscheidenheid aan verbindingen te bereiden én te laten screenen op biologische activiteit.

Oorspronkelijk werden grote combinatorische bibliotheken van peptiden opgebouwd die konden *gescreend* worden tegen een bepaalde receptor of een specifiek enzyme. Peptiden hebben echter een beperkt nut als geneesmiddel omdat ze in het algemeen niet via de mond kunnen worden ingenomen en omdat ze snel fysiologisch worden afgebroken. In de tweede helft van de negentiger jaren verhoogde (mede door de uitbreiding van het beschikbare arsenaal aan vastefasereacties) de interesse naar actieve verbindingen met een lager moleculair gewicht. Zo werden indrukwekkende bibliotheken van farmaceutisch interessante heterocyclische verbindingen gesynthetiseerd (bijvoorbeeld benzodiazepines, hydantoïnes, indolen en benzimidazolen) [245] . Desondanks bleef de verwachte uitstroom van nieuwe leadverbindingen uit. Nadere analyse door een aantal groepen wees erop dat de aangelegde bibliotheken té complex waren[246].

Recentere inzichten benadrukken nu meer het belang van zogenaamde *"privileged (sub)structures"*: dit zijn klassen van verbindingen die affiniteit vertonen voor verschillende types receptoren[247]. Design van een dergelijke preferentiële *scaffold* als centrale basisarchitectuur in een aangelegde bibliotheek blijkt een aanzienlijk hogere kans te geven tot het vinden van verschillende leadverbindingen met uiteenlopende activiteiten jegens een verscheidenheid aan receptoren. Zo werd door de Ellman-groep uit een bibliotheek van 1,4-benzodiazepine-2-onen een aantal leden geïdentificeerd met affiniteit voor sterk uiteenlopende farmaceutisch interessante *targets,* zoals de CCK-A receptor en pp60$^{s\text{-}src}$ tyrosinekinase, en vertoonden sommige leden ook anti-autoimmuniteitswerking[248].

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[245] a. Dolle, R. E.; Nelson, K. H. *J. Comb. Chem.* **1999**, *1*, 235-282. b. Dolle, R. E. *J. Comb. Chem* **2000**, *2*, 383-433. c. Dolle, R. E. *J. Comb. Chem* **2001**, *3*, 447-517. d. Dolle, R. E. *J. Comb. Chem* **2002**, *4*, 369-418. e. Dolle, R. E. *J. Comb. Chem* **2003**, *5*, 693-753. f. Dolle, R. E. *J. Comb Chem* **2004**, *6*, 623-679 g.Dolle, R. E. *J. Comb Chem* **2005**, 7, 739-798 h. Dolle, R. E.; Le Bourdonnec, B.; Morales, G. A.; Moriarty, K.J.; Salvino, J. M. *J. Comb Chem* **2006**, *8*, 598-635

[246] Teague, S. J.; Davis, A. M.; Leeson, P. D.; Oprea, T. *Angew. Chem. Int. Ed. Engl.* **1999**, *38*, 3743-3748.

[247] a) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893-930. b) Nicolaou, K. C.; Pfefferkorn, J. A.; Roecker, A. J.; Cao, G.-Q.; Barluenga, S.; Mitchell, H. J. *J. Am. Chem. Soc.* **2002**, *122*, 9939-9953.

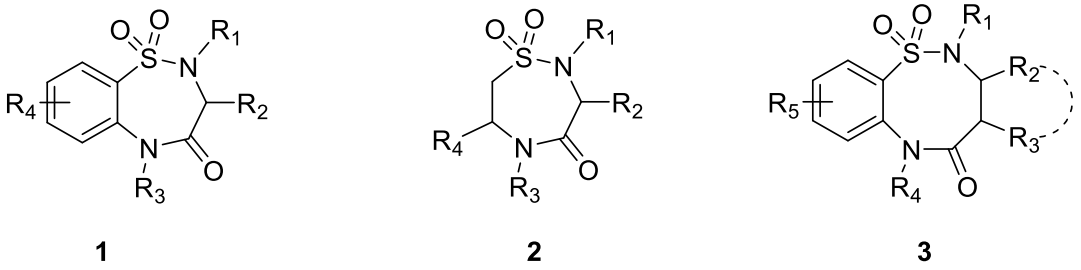
[248] a) Bunin, B. A.; Plunkett, M. J.; Ellman, J. A. *Proc. Natl. Acad. Sci.* **1994**, *91*, 4708-4712. b) Thompson, L. A.; Ellman, J. A. *Acc. Chem. Res.* **1996**, *96*, 555-600.

2 DOELSTELLING

Verklaringen voor het bestaan van dergelijke preferentiële (sub)structuren liggen in de ruimtelijke, elektronische en fysicochemische eigenschappen van de betrokken structuren. Vooral non-covalente interacties van de centrale *scaffold* met het peptideskelet van de receptoren blijken van belang te zijn. Onderzoek en vergelijking van structuren van gekende bibliotheken, hits, *leads* en gekende geneesmiddelen leidde tot interessante bruikbare conclusies voor de design van *lead*-gerichte bibliotheken.

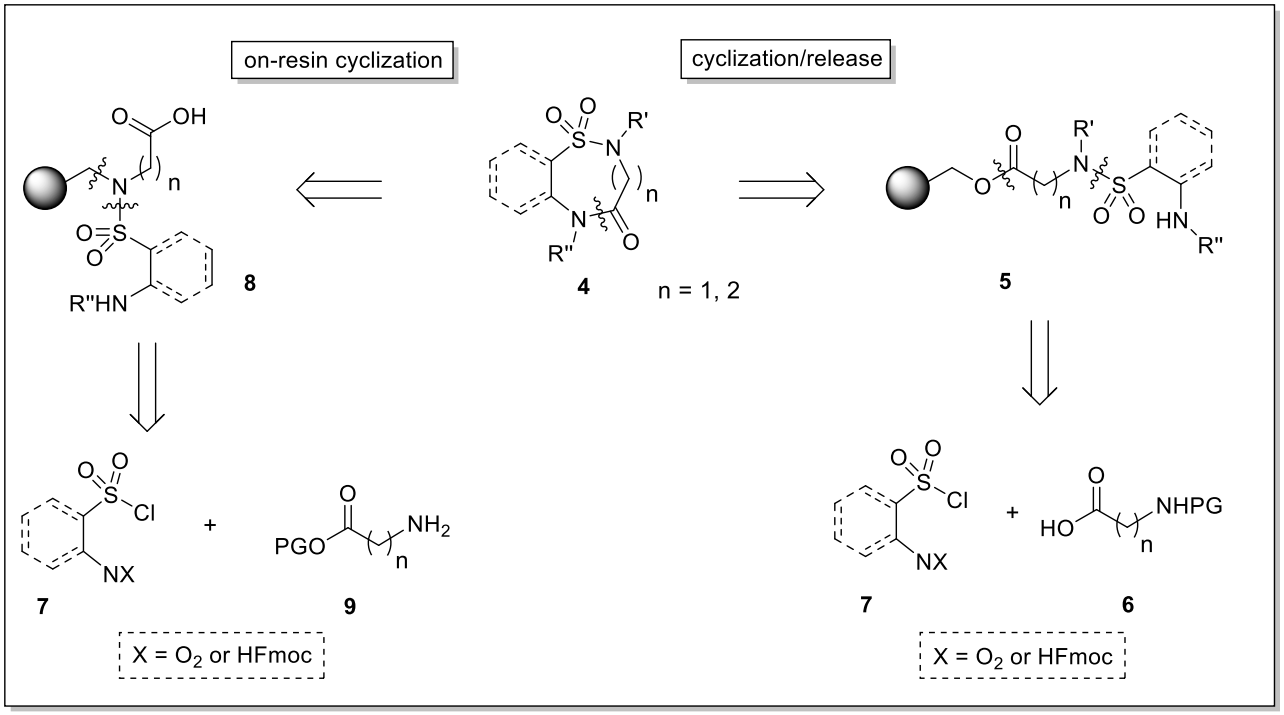
Bicyclische en tricyclische systemen blijken hier als ideale na te streven structuren naar voor te komen. Ze bezitten een relatief laag moleculair gewicht, en hun cyclische structuur voorziet in de nodige moleculaire starheid voor betere receptorbinding. De centrale *scaffold* zorgt voor non-specifieke bindingscapaciteit tegen een uiteenlopende reeks receptoren, terwijl de substituenten op de *scaffold* verantwoordelijk zijn voor de receptorspecificiteit.

Wij willen bij deze trend aansluiten en op zoek gaan naar nieuwe geprefereerde structuren. We denken hierbij aan 2,3-dihydro-1,2,5-benzothiadiazepine-4(5*H*)-on-1,1-dioxiden (**1**), 1,2,5-thiadiazepane-4-on-1,1-dioxiden (**2**), 3,4-dihydro-2*H*-1,2,6-benzothiadiazocine-5(6*H*)-on-1,1-dioxiden (**3**) zoals voorgesteld in figuur 1.



Figuur 1. Overzicht doelstructuren

De door ons voorgestelde vastefasesynthesestrategie op basis van commerciële of eenvoudig te bereiden bouwstenen zou moeten leiden tot structureel diverse bibliotheken, waarin het basisskelet op verschillende plaatsen kan worden gesubstitueerd. Voor elk type verbindingen voorzien we bovendien telkens twee complementaire synthesewegen om maximale diversiteit in de eindverbindingen te kunnen waarborgen (figuur 2). De cruciale stap is de vorming van de lactamfunctie, waarbij de zeven- of achtring wordt gesloten. Al naar gelang van de functionele groep waarmee het opgebouwde dipeptide aan het hars is gekoppeld, blijft het cyclisatieproduct ofwel aan het hars gekoppeld ("on-resin"-cyclisatie), of wordt het simultaan met de ringsluiting afgesplitst ("cyclization-release"-strategie).



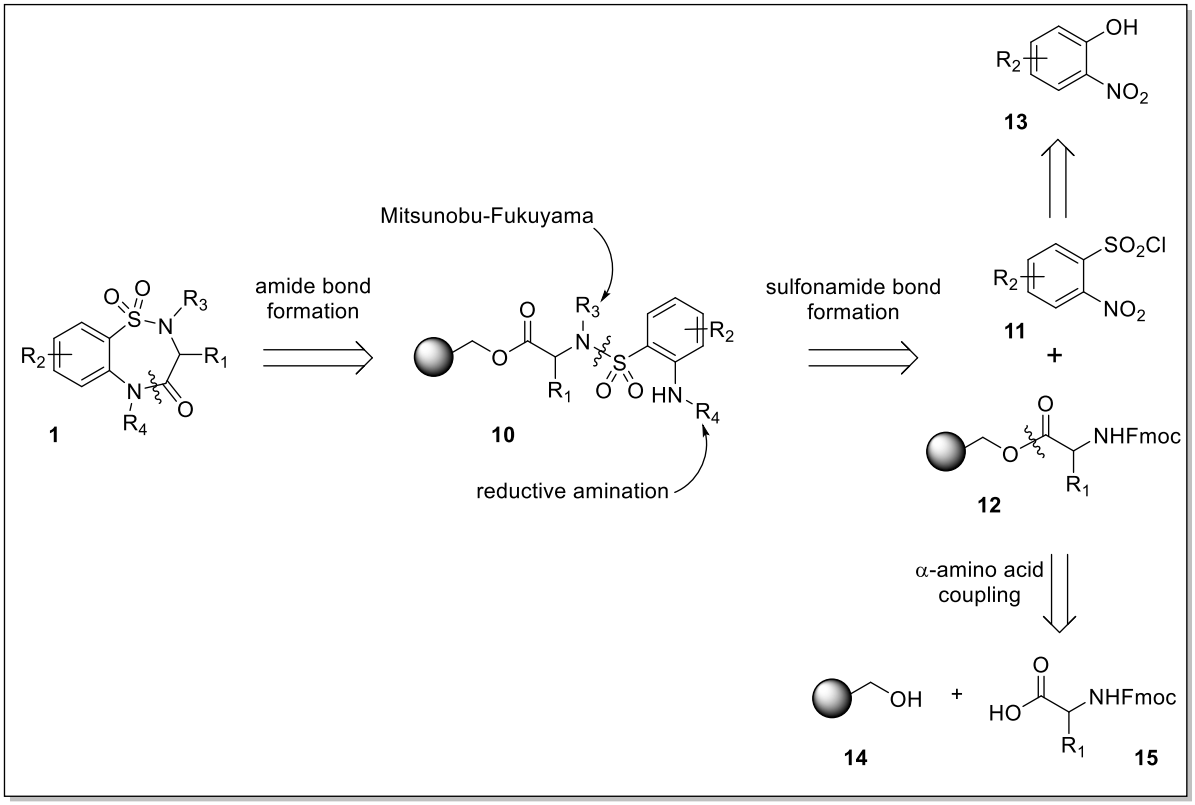
Figuur 2. Retrosynthetisch overzicht van de "cyclization/release" en "on-resin cyclization" strategie

3 SYNTHESE

3.1 SYNTHESE VAN DE 2,3-DIHYDRO-1,2,5-BENZOTHIADIAZEPIN-4(5*H*)-ON-1,1-DIOXIDES VIA DE CYCLIZATION/RELEASE-STRATEGIE

3.1.1 RETROSYNTHETISCH OVERZICHT

Zoals reeds werd voorgesteld in het algemene retrosyntheseschema, is de meest logische eerste disconnectie deze van de amidebinding. Dit geeft aanleiding tot ringprecursor **10**, die kan opgebouwd worden uit 2 centrale bouwstenen namelijk Fmoc-beschermde α-aminozuren **15** en 2-nitrobenzeensulfonylchlorides **13**. Verdere decoratie van de scaffold op de N2 en N5 positie, zal respectievelijk via een Mitsunobu-Fukuyama alkylering en reductieve aminering verlopen.



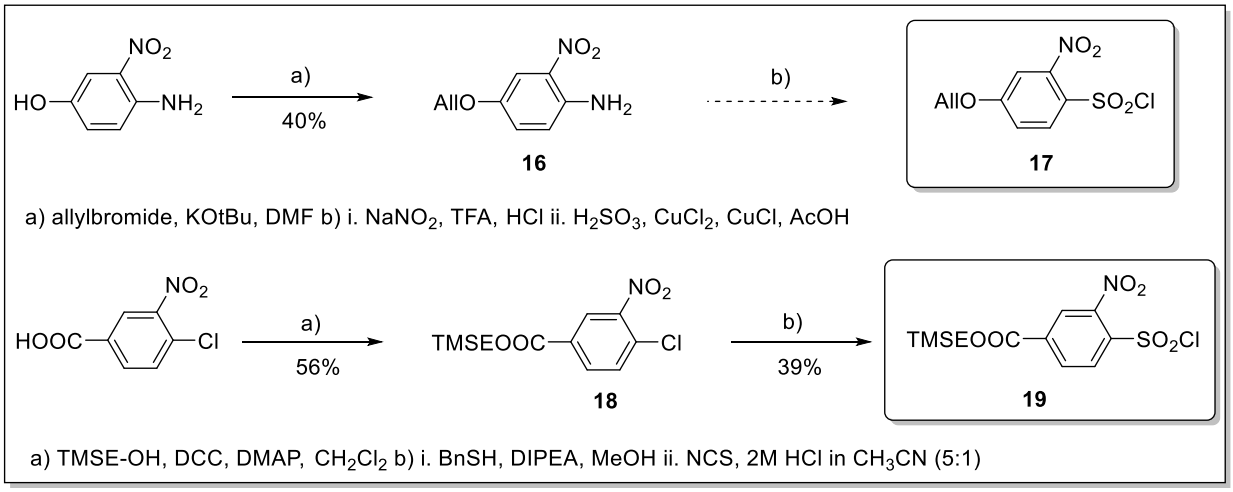
Figuur 3. Retrosynthetisch overzicht 2,3-dihydro-1,2,5-benzothiadiazepin-4(5*H*)-on-1,1-dioxides **1**

3.1.2 SYNTHESE VAN 2-NITROBENZEENSULFONYLCHLORIDES

Voor de synthese van benzothiadiazepines **1** en benzothiadiazocines **3** wordt gebruik gemaakt van 2-nitrobenzeensulfonylchlorides **11** als bouwstenen. Aangezien deze niet commercieel verkrijgbaar zijn, werd in het eerste projectvoorstel een synthese opgesteld uitgaande van 4-amino-3-nitrofenol [249] en 4-chloor-3-nitrobenzoëzuur [250] (figuur 4). Beide syntheseroutes

[249] Andrews, S.P.; Ladlow, M. *J. Org. Chem.* **2003**, *68*, 5525-5533.
[250] Dener, J.M.; Fantauzzi,P.P.; Kshirsagar, T.A.; Kelly, D.E.; Wolfe, A.B. Org. Proc. Res. & Devel. **2001**, *5*, 445-449.

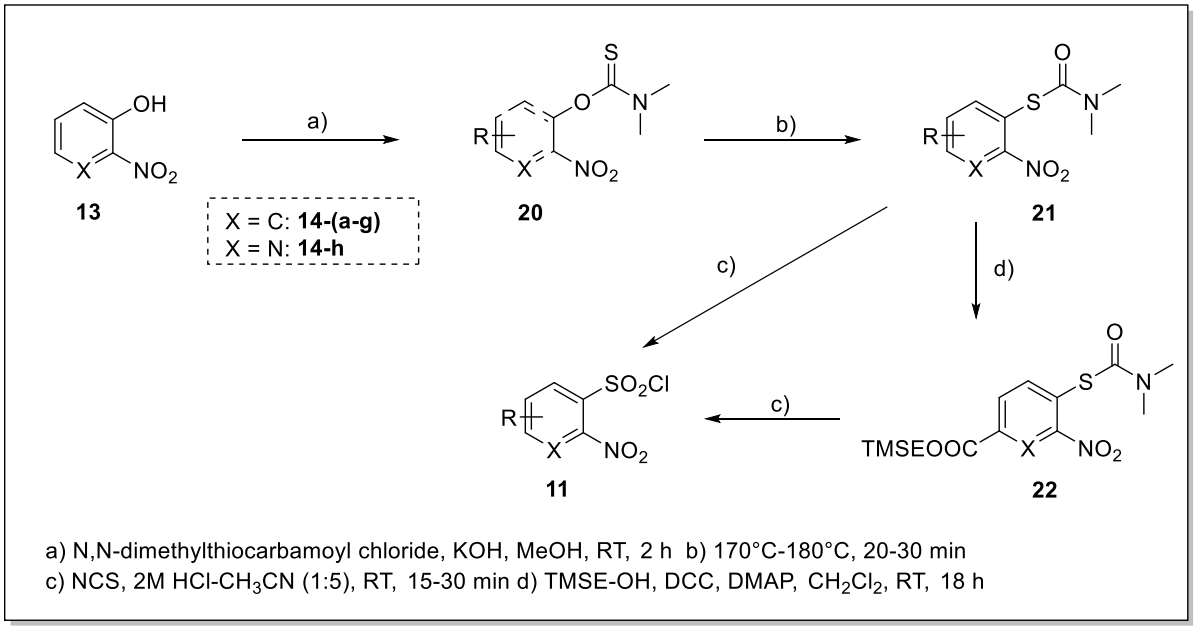
leverden echter niet de gewenste resultaten op. 4-amino-3-nitrofenol kon worden beschermd tot zijn respectievelijke allylether **16**, omzetting naar sulfonylchloride 18 via een Sandmeyer type reactie gaf echter geen product. De bescherming van 4-chloor-2-nitrobenzoëzuur als 2-(trimethylsilyl)ethylester **18**, gevolgd door een nucleofiel aromatische substitutie tot thiobenzylether verliep probleemloos. De oxidatieve chlorering met NCS in zuur midden gaf het gewenste sulfonylchloride **19**, echter met onvoldoende opbrengst en zuiverheid.



Figuur 4. Initieel voorgestelde syntheseroute voor de 2-nitrobenzeensulfonylchlorides

Daarom werd een tweede syntheseroute voorgesteld, uitgaande van commercieel verkrijgbare 2-nitrofenolen [251] (figuur 5). Omzetting van de nitrofenolen tot hun respectievelijke O-thiocarbamaten, gevolgd door een Newman-Kwart omlegging levert de overeenkomstige S-thiocarbamaten **21**. Oxidatieve chlorering van deze intermediairen tenslotte geeft aanleiding tot de gewenste sulfonylchlorides **11**. Deze methode bleek wel succesvol, met een achttal nieuwe bouwstenen als resultaat (tabel 1).

[251] a) Percec, V.; Bera, T. K.; De, B. B.; Sanai, Y.; Smith, J.; Holerca, M. N.; Barboiu, B. *J. Org. Chem.* **2001**, **66**, 2104-2117 b) Nishiguchi, A.; Maeda, K.; Miki, S. *Synthesis* **2006**, *24*, 4131-4134



Figuur 5. Synthese van de 2-nitrobenzeenzulfonylchlorides **11**

Product	R	20	21	11
a	4-Cl	92%	99%	84%
b	4-Br	97%	97%	83%
c	6-Br	56%	98%	85%
d	3-F	89%	95%	94%
e	5-F	94%	99%	71%
f	4-COOTMSE	29%	93%	38%[a]
g	4-CHO	83%[b]	95%	95%
h	H	76%	92%	80%

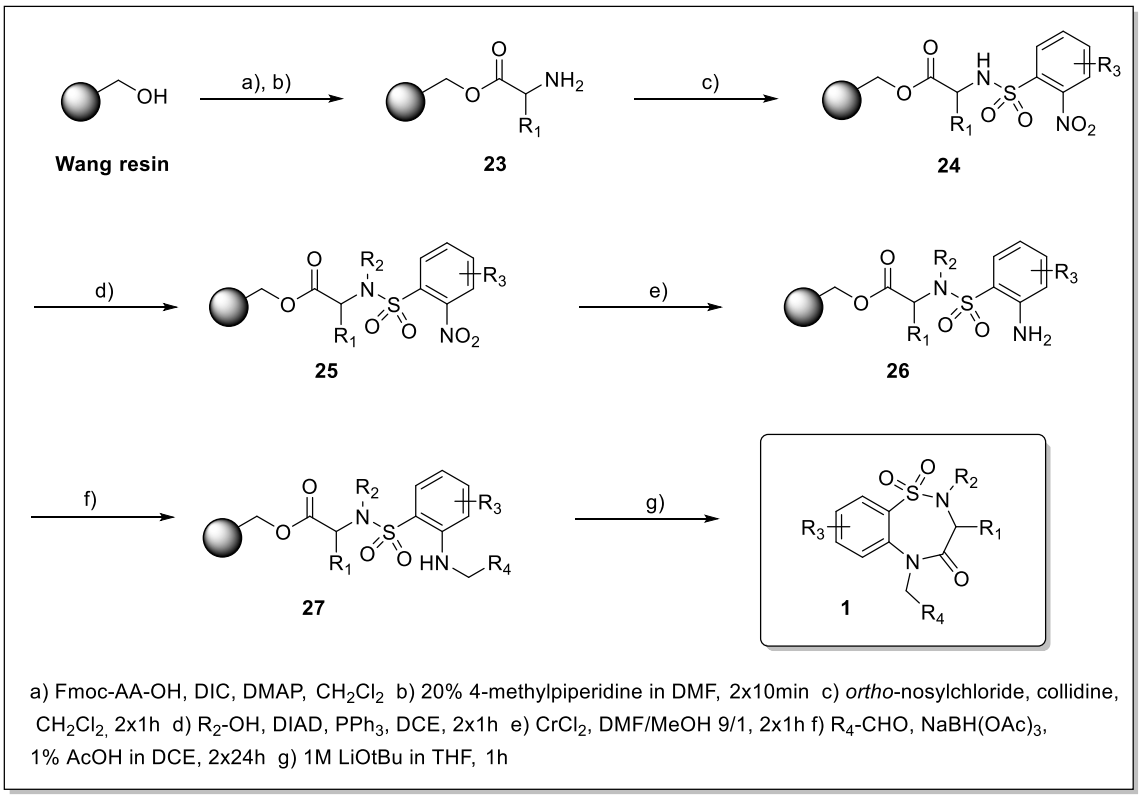
[a] rendement over 2 stappen: TMSE-bescherming en oxidatieve chlorering

[b] rendement over 2 stappen: O-thiocarbamoylering en acetal ontscherming

Tabel 1. Overzicht van de gesynthetiseerde 2-nitrobenzeensulfonylchlorides **11-(a-h)**

3.1.3 SYNTHESE 2,3-DIHYDRO-1,2,5-BENZOTHIADIAZEPIN-4(5H)-ON-1,1-DIOXIDES IN BASISCH MIDDEN

De synthese van de benzothiadiazepines **1** werd uitgevoerd zoals beschreven in het oorspronkelijke project (figuur 6). De condities van elke reactie werden geoptimaliseerd op de modelmolecule **1c** (tabel 2) en vervolgens toegepast op de synthese van alle andere analogen. Door gebruik te maken van verschillende α-aminozuren, alcoholen en 2-nitrobenzeensulfonylchlorides zijn we er in geslaagd de *scaffold* in 3 dimensies te gaan variëren. De diversificatie van onze doelmoleculen op de N5 positie werd ook uitgevoerd, maar wordt in een verdere paragraaf besproken omdat er problemen optreden bij de cyclisatie (vide infra).



Figuur 6. Syntheseroute via de cyclization/release strategie

Zo werden op deze wijze uiteindelijk een 22-tal benzothiadiazepines **1** gesynthetiseerd (Tabel 2-A & 2-B). Alle verbindingen werden opgezuiverd met kolomchromatografie of waar mogelijk door omkristallisatie.

Product	R_1	R_2	Rendement (%)
a	H	H	39
b	iPr	H	16
c	Bn	Me	38
d	Bn	CH_2Bn	54
e	Bn	iBu	41
f	Bn	$C_{10}H_{21}$	35
g	Bn	2-morfolinoethyl	33
h	H	Bn	26
i	$(CH_2)_4NHBoc$	Me	54
j	$CH_2Im(Trt)$	Me	38
k	3-indolyl(Boc)methyl	Me	57
l	3-indolylmethyl	Me	44
m	3-indolyl(Boc)methyl	Bn	62
n	Me	Me	58

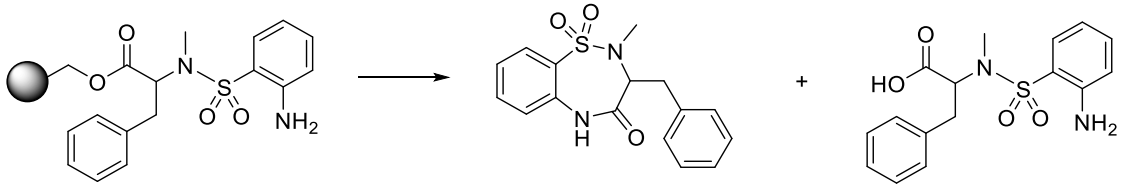
Tabel 2-A. Bibliotheek van 2,3-dihydro-1,2,5-benzothiadiazepin-4(5*H*)-on-1,1-dioxides gediversifieerd op 2 posities

Product	R_1	R_2	X	R_3				Rendement
				6	7	8	9	(%)
o	iBu	Me	C	H	Cl	H	H	40
p	Bn	Me	C	H	Cl	H	H	23
q	H	Me	C	H	Cl	H	H	48
r	Bn	Me	C	H	Br	H	H	11
s	Bn	Me	C	H	H	F	H	24
t	H	Me	C	H	Br	H	H	56
u	H	Me	C	H	H	F	H	61
v	iBu	Bn	C	H	H	F	H	46
w	H	H	N	H	H	H	H	10
x	Bn	Me	N	H	H	H	H	5
y	iBu	Bn	N	H	H	H	H	18
z	Bn	Me	C	F	H	H	H	19
aa	4-O*t*BuBn	iBu	C	H	Br	H	H	23

Tabel 2-B. Bibliotheek van 2,3-dihydro-1,2,5-benzothiadiazepin-4(5*H*)-on-1,1-dioxides gediversifieerd op 3 posities

3.1.4 SYNTHESE 2,3-DIHYDRO-1,2,5-BENZOTHIADIAZEPIN-4(5H)-ON-1,1-DIOXIDES IN ZUUR MIDDEN

Hoewel de ringsluiting in basisch midden vlot verliep voor de meeste substraten, werden toch enkele problemen vastgesteld. Zo bleek dat bij gebruik van serine als bouwsteen eliminatie optrad van de *tert*-butyl- of benzylbeschermde alcoholzijketen. Een andere factor waarmee rekening moest gehouden worden, was de racemisatie aan ons stereocenter. De basische condities bleken namelijk een negatief effect te hebben op de *ee* van ons eindproduct. Om deze problemen te vermijden, werd geopteerd om de ringsluiting in zuur midden te gaan uitvoeren[252]. Zoals beschreven in tabel 3 werden verschillende condities getest, maar zonder resultaat. Het probleem lag bij de zuurgevoeligheid van het Wang hars: TFA is een te sterk zuur en zorgde voor een vroegtijdige afsplitsing tot **28**, AcOH bleek te zwak om de ringsluiting te induceren.



26 **1-c** **28**

Test	Solvent/zuur	[T]	Tiid	Resultaat
A	50/50 DCE/AcOH	RT	16 h	geen product
B	20/80 DCE/AcOH	60°C	30 min	geen product

[252] Laustsen, L. S.; Sams, C. K. *J. Comb. Chem.* **2007**, *9*, 1094-1103

C	20/80 DCE/AcOH	100°C	15 min	**28** + spoor **1-c**
D	20/80 DCE/AcOH	100°C	30 min	**28**
E	50/50 THF/AcOH	100°C	15 min	**28**
F	90/10 DCE/TFA	RT	2 h 30 min	**28** + spoor **1-c**
G	80/20 DCE/TFA	RT	6 h	**28**
H	80/20 DCE/TFA	RT	21 h	**28**
I	50/50 THF/HCOOH	100°C	15 min	**28**

Tabel 3. Overzicht condities testreacties ringsluiting in zuur midden

Daarom werd overgeschakeld op hydroxymethyl-polystyreen (HM-PS), een hars waarbij zelfs onder sterk zure condities geen afsplitsing optreedt. Na uitvoeren van de synthese volgens de reeds toegepaste procedure en testen van een aantal afsplitsingscondities, werd met succes een ringgesloten product bekomen door gebruik te maken van een 50/50 THF/TFA mengsel bij 100°C onder microgolfverwarming (tabel 4).

Test	Solvent/Zuur	[T]	Tijd	Resultaat
A	95/5 DCE/TFA	60°C	30 min	**28**
B	80/20 DCE/TFA	60°C	30 min	**28**
C	80/20 DCE/TFA	60°C	30 min	**28**
D	50/50 DCE/TFA	60°C	30 min	**28** + spoor **1-c**
E	50/50 THF/TFA	60°C	30 min	**28**
F	50/50 THF/TFA	100°C	30 min	**1-c** + spoor **28**
G	80/20 THF/TFA	100°C	30 min	**1-c** + **28**
H	50/50 THF/TFA	80°C	30 min	**1-c** + **28**

Tabel 4. Overzicht condities testreacties ringsluiting in zuur midden op HM-PS

Uiteindelijk werden 11 benzothiadiazepines **1** op deze wijze gesynthetiseerd, waarvan het overzicht kan teruggevonden worden in onderstaande tabel (tabel 5). Een nader onderzoek van de ringsluiting leerde ons echter dat de veronderstelde cyclization/release reactie eigenlijk bestond uit een vroegtijdige afsplitsing en een ringsluiting in oplossing. Deze vaststelling gecombineerd met de relatief zware reactieomstandigheden voor ringsluiting, maakten deze methode minder geschikt dan de afsplitsing in basisch midden. In het verdere verloop van het project werd dan ook de ringsluiting in basisch midden als standaardmethode toegepast.

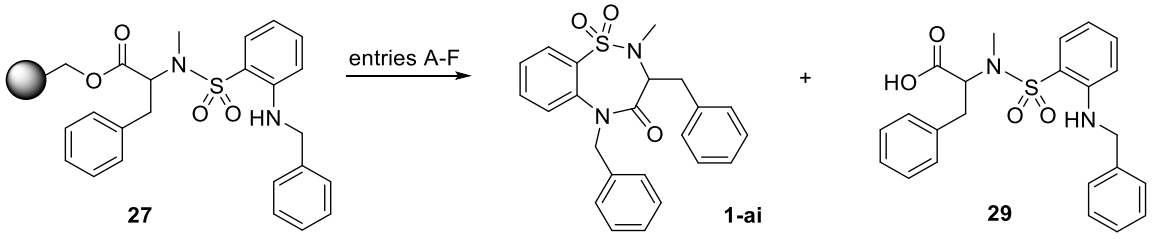
Product	R_1	R_2	R_3		Rendement
			7	**8**	
ab	iBu	Bn	H	H	12%
ac	iBu	2-morfolinoethyl	H	H	10%
o	Bn	Me	Cl	H	2%
r	Bn	Me	Br	H	10%
c	Bn	Me	H	H	10%
ad	Bn	Bn	H	H	22%
g	Bn	2-morfolinoethyl	H	H	9%

ae	H	Me	H	H	42%
af	H	CH_2Bn	H	H	47%
ag	H	iBu	H	H	32%
ah	H	$C_{10}H_{21}$	H	H	10%

Tabel 5. Overzicht 2,3-dihydro-1,2,5-benzothiadiazepin-4(5*H*)-on-1,1-dioxides ringgesloten onder zure condities

3.1.5 N5-ALKYLERING

Op onze scaffold kan ook een vierde punt van diversiteit ingevoerd worden via reductieve aminering van de anilinefunctie, door gebruik te maken van $NaBH(OAc)_3$[253] zoals beschreven in figuur 6. Zo werden een ethyl, pentyl en benzylzijketen ingevoerd op het harsgebonden product **27**. De daaropvolgende ringsluiting met 1M LiOtBu in THF bleek echter niet meer voor de hand liggend, zelfs niet met bijkomende verwarming (tabel 6). Ook onder sterkere basische condities, 2 eq NaH in THF, bleek geen ringgesloten product gevormd te worden. Een overschakeling naar de reeds met succes gebruikte zure ringsluitingscondities bleek eveneens geen aanleiding te geven tot de gewenste doelmoleculen, enkel sporen van open product **29** werd teruggevonden. Door gebruik te maken van de "cyclization/release"-strategie, slaagden we er dus niet in om de beoogde doelmoleculen te synthetiseren. Een derde optie lag in de omschakeling naar de "on-resin cyclization"-strategie, wat een activatie van het carbonzuur toelaat en dus een vlottere ringsluiting zou induceren (vide infra).



Test	Omstandigheden	Resultaat
A	1 M LiOtBu in THF, rt, 30 min - 4 h	no product
B	1 M LiOtBu in THF, 60°C, MW, 30 min	no product
C	DMF, 80°C, MW, 30 min	no product
D	THF/TFA 50/50, 100°C, MW, 30 min	carboxylic acid **29**
E	2 eq NaH, THF, 20 h	no product
F	5 eq 2-pyridone, THF, 60°C, MW, 16 h	no product

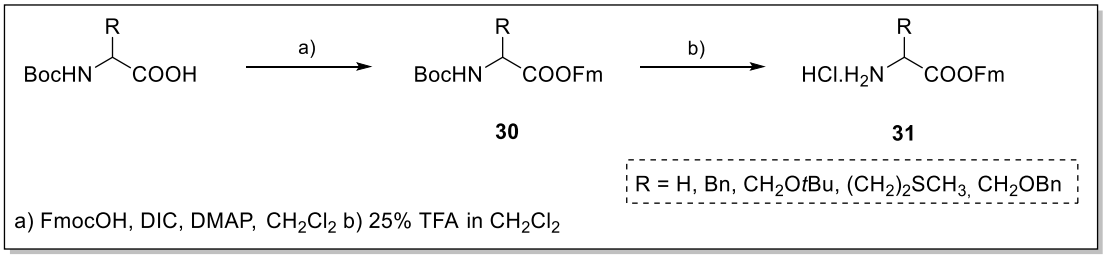
Tabel 6. Overzicht testreacties voor de ringsluiting tot N5 gealkyleerde 2,3-dihydro-1,2,5-benzothiadiazepin-4(5*H*)-one-1,1-dioxide **1-ai**

[253] Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849-3862

3.2 SYNTHESE 2,3-DIHYDRO-1,2,5-BENZOTHIADIAZEPIN-4(5*H*)-ON-1,1-DIOXIDES VIA DE "ON-RESIN CYCLIZATION"-STRATEGIE

3.2.1 SYNTHESE VAN FLUORENYLMETHYL BESCHERMDE AMINOZUREN

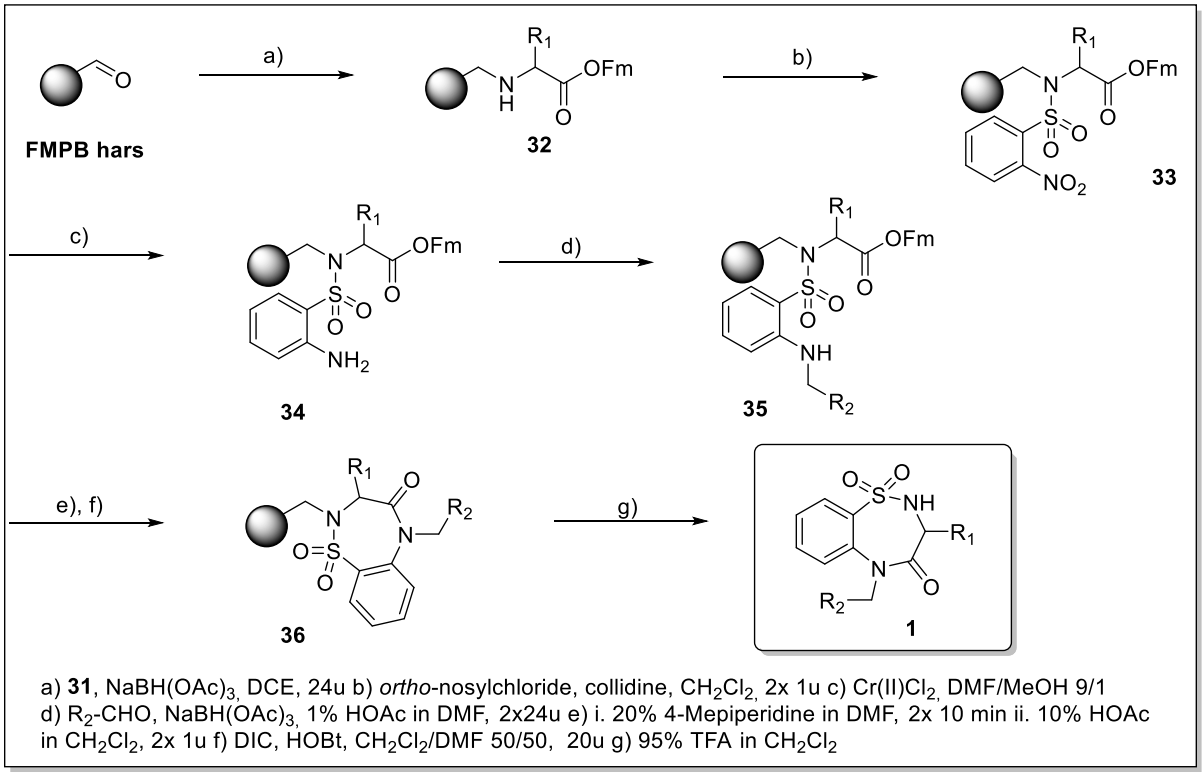
Voor het toepassen van de "on-resin cyclization"-strategie bij de synthese van de doelmoleculen, was er nood aan enkele fluorenylmethyl beschermde α-aminozuren. Een korte tweestapssynthese (figuur 7), uitgaande van Boc beschermde α-aminozuren, gaf aanleiding tot de gewenste bouwstenen.



Figuur 7. Synthese fluorenylmethyl beschermde aminozuren

3.2.2 SYNTHESE 2,3-DIHYDRO-1,2,5-BENZOTHIADIAZEPIN-4(5*H*)-ON-1,1-DIOXIDES

Naast de "cyclization/release"-strategie, werd in het oorspronkelijke project ook een alternatieve syntheseroute beschreven waarbij de ringsluiting "on-resin" gebeurde (figuur 8). Deze strategie heeft als voordeel dat het carbonzuur **36** kan worden geactiveerd en de ringsluiting dus vlotter zou moeten verlopen. Voor de opbouw van de benzothiadiazepines volgens deze strategie werd gebruik gemaakt van bouwstenen **31**, *ortho*-nosylchlorides en aldehydes. De synthese zelf werd uitgevoerd op een andere vaste drager namelijk aminomethylpolystyreen gefunctionaliseerd met een 4-(4-formyl-3-methoxyfenoxy)boterzuurlinker (FMPB-linker).



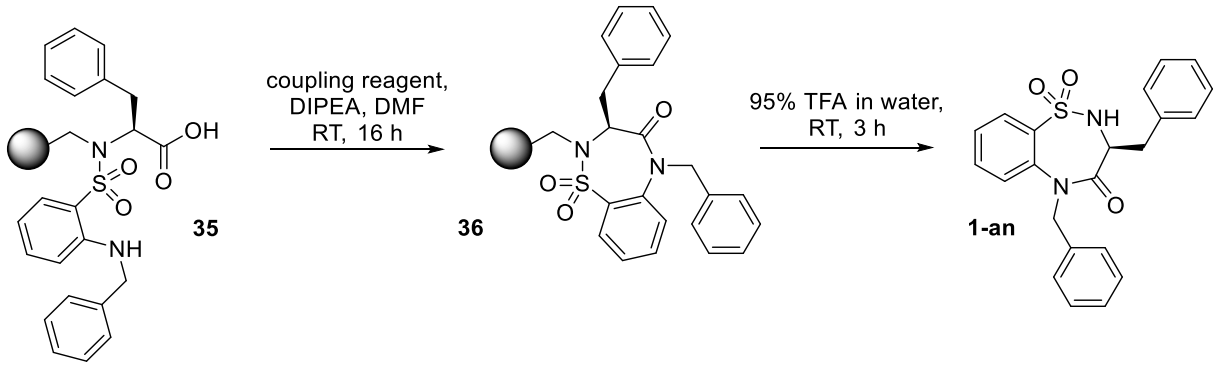
Figuur 8. Synthese 2,3-dihydro-1,2,5-benzothiadiazpin-4(5*H*)-on-1,1-dioxides via de "on-resin" strategie

Na optimalisatie van de verschillende reactiestappen, werd via deze syntheseroute een viertal benzothiadiazepines gesynthetiseerd zonder substituent op de N5 positie. Wegens de kleine schaal waarop deze syntheses getest werden, werd er geen rendement bepaald van de bekomen producten en gebeurde de analyse uitsluitend via LC-MS. Enkel product **1-ae** werd op voldoende grote schaal uitgevoerd om verdere opzuivering en NMR analyse toe te laten. De resultaten worden weergegeven in onderstaande tabel.

product	R_1	rendement
1-ab	H	<1%
1-ac	Bn	4%
1-ad	$(CH_2)_2SCH_3$	<1%
1-ae	CH_2OBn	6%

Tabel 7. Overzicht gesynthetiseerde benzothiadiazepines via de “on-resin cyclization”-strategie

Het doel voor het toepassen van deze strategie echter, was de ringsluiting van N5 gealkyleerde benzothiadiazepines. Daarvoor werd ringsluitingprecursor 35 behandeld met verschillende koppelingsreagentia, samengevat in tabel 8. Na analyse bleek dat enkel PyBrop aanleiding gaf tot het gewenste ringgesloten product **1-an**. Hoewel het gewenste product werd bekomen, bedroeg het totaalrendement maar 4%. Daarom werd besloten om de synthese van de N5 gealkyleerde producten toch nog via een alternatieve syntheseroute aan te pakken, namelijk via een afsplitsing van het product in oplossing gevolgd door een ringsluiting in oplossing (vide infra).

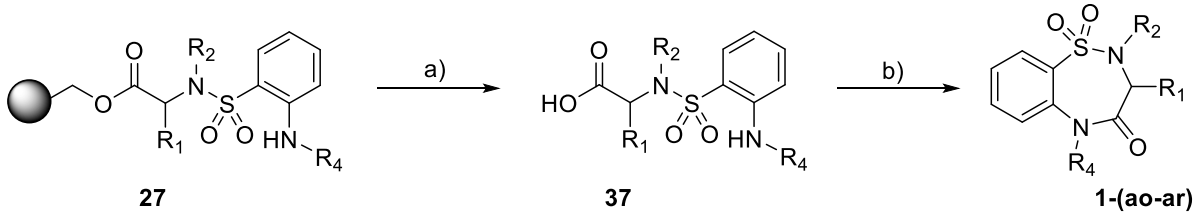


Test	Reagens	Resultaat
A	BOP	spoor **1-an** + spoor **35-an** + HOBt
B	HATU	spoor **1-an** + **35-an** + HOBt
C	HCTU	spoor **1-an** + **35-an** + 6-ClHOBt
D	PyBrOP	**1-an** + spoor **35-an**
E	IIDQ	**35-an**

Tabel 8. Testcondities "on-resin"-ringsluiting

3.3 SYNTHESE 2,3-DIHYDRO-1,2,5-BENZOTHIADIAZEPIN-4(5*H*)-ON-1,1-DIOXIDES VIA DE RINGSLUITING IN OPLOSSING

Net als bij de "on-resin" strategie kan via deze methode de ringsluiting geinduceerd worden door de activatie van het carbonzuur, waardoor de ringsluiting vlotter zou moeten verlopen. De syntheseroute verloopt identiek als bij de cyclization/release strategie, maar de laatste stap wordt hierbij vervangen door de afsplitsing van de ringsluitingsprecursor **37** in zuur midden. Na opzuivering van het afgesplitste product, werd de ringsluiting in oplossing met succes getest door gebruik te maken van het koppelingsreagens PyBrOP. Vervolgens werden via deze methode 4 benzothiadiazepines **1** gesynthetiseerd, weergegeven in tabel 9.



a) 95% TFA in H_2O, RT, 3 h b) PyBrOP, DIPEA, DMF, RT, 4 h

Product	R_1	R_2	R_4	Rendement 31	Rendement 1
ao	H	Me	*n*-pentyl	50%	60%

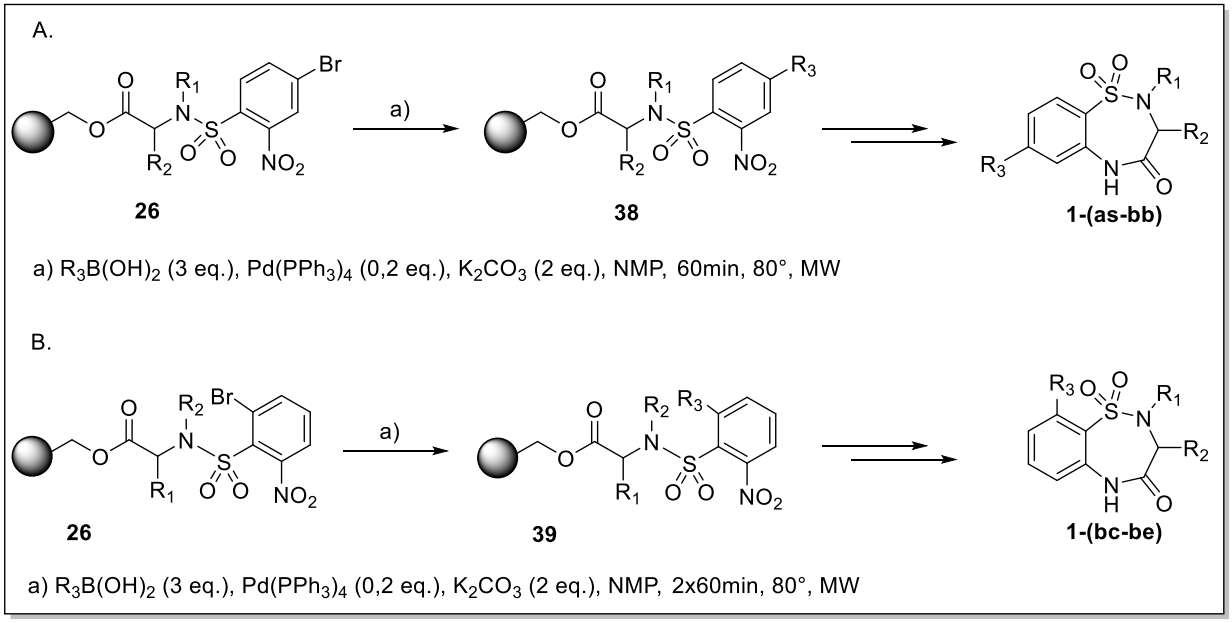
ap	H	Bn	*n*-pentyl	32%	76%
aq	H	Me	Bn	49%	72%
ar	H	Bn	Bn	51%	65%

Tabel 9. Overzicht rendementen van de afsplitsing en ringsluiting in oplossing

3.4 VERDERE DERIVATISATIE VAN DE 1,2,5-BENZOTHIADIAZEPIN-4(5*H*)-ON-1,1-DIOXIDES

3.4.1 SYNTHESE VAN 7- EN 9-ARYL-2,3-DIHYDRO-1,2,5-BENZOTHIADIAZEPIN-4(5H)-ONE-1,1-DIOXIDES

De introductie van 4-bromo-2-nitrobenzeensulfonylchloride **11-b**, een van onze bouwstenen, liet ons toe om tijdens de synthese een "on-resin" Suzuki cross-coupling reactie uit te voeren. Uitgaande van reeds gekende literatuurprocedures[254], werden een aantal cross-couplingcondities getest op ons harsgebonden product. Om de reactietijden te beperken, werd ervoor gekozen om de reacties uit te voeren onder microgolfverwarming[14]. De optimale condities worden hieronder voorgesteld (figuur 9-A). Via deze route konden uiteindelijk een 10-tal nieuwe 7-arylbenzothiadiazepines worden gesynthetiseerd (tabel 10). Ook na het inbouwen van 6-bromo-2-nitrobenzeensulfonylchloride **11-c**, bleek het mogelijk om onder quasi identieke reactieomstandigheden een Suzuki-koppeling uit te voeren (figuur 9-B). Dit resulteerde in drie 9-arylbenzothiadiazepines, weergegeven in tabel 10-A & 10-B.



Figuur 9-A & B. "On-resin" Suzuki cross-coupling

Product	R_1	R_2	R_3	Rendement
as	H	Me	Ph	8%
at	Bn	Me	Ph	14%

[254] a) Backes, B. J.; Ellman, J. A. *J. Am. Chem. Soc.* **1994**, *116*, 11171-11172 b) Yoo, S.; Seo, J.; Yi, K.; Gong, Y. *Tetrahedron Lett.* **1997**, *38*, 1203-1206

au	Bn	Me	4-MeOPh	19%
av	iBu	Me	4-iBuOPh	39%
aw	iBu	Me	3,5-F_2Ph	5%
ax	3-indolyl(Boc)methyl	Me	Ph	4%
ay	iBu	Bn	Ph	22%
az	CH_2Ph(4-O*t*Bu)	iBu	3-thiofenyl	15%
ba	CH_2Ph(4-OH)	iBu	3-thiofenyl	11%
bb	CH_2Ph(4-O*t*Bu)	Me	2-MeOPh	21%

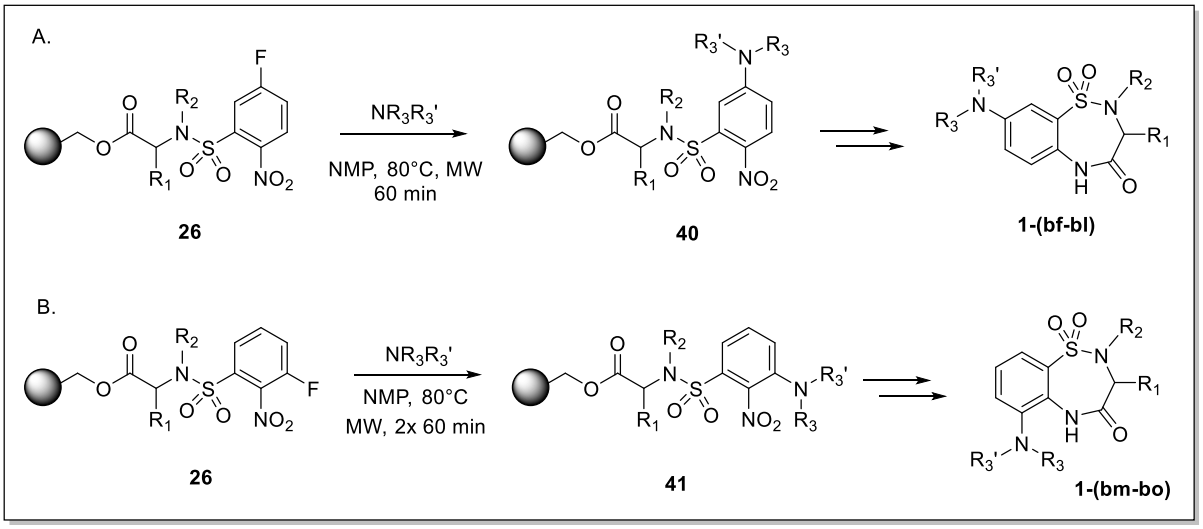
Tabel 10-A. Overzicht 7-aryl-1,2,5-benzothiadiazepin-4(5*H*)-on-1,1-dioxides

Product	R_1	R_2	R_3	Rendement
bc	iBu	Me	Ph	20%
bd	iBu	Me	4-(OiBu)Ph	21%
be	iBu	Me	3-thiophenyl	22%

Tabel 10-B. Overzicht 9-aryl-1,2,5-benzothiadiazepin-4(5*H*)-on-1,1-dioxides

3.4.2 SYNTHESE VAN 6- EN 8-AMINOALKYL-2,3-DIHYDRO-1,2,5-BENZOTHIADIAZEPIN-4(5H)-ONE-1,1-DIOXIDES

De koppeling van 3-fluoro-2-nitrobenzeensulfonylchloride **11-e** en 5-fluoro-2-nitrobenzeensulfonylchloride **11-d** bood ook de mogelijkheid om onze doelmolecule nog verder te decoreren. De fluoro-substituent zou immers door zijn gunstige plaatsing ten opzichte van de nitrogroep (*ortho* of *para*) waarschijnlijk aanleiding kunnen geven tot een nucleofiele aromatische substitutie S_NAr. Na een aantal testreacties, gebaseerd op precedenten vanuit de literatuur, kon inderdaad een volledige substitutie bereikt worden door het hars via microgolven te verwarmen in aanwezigheid van een geschikt nucleofiel en NMP als solvent. Op deze wijze werden drie 6-aminoalkylbenzothiadiazepines en zeven 8-aminoalkylbenzothiadiazepines gesynthetiseerd.



Figuur 10-A en **10-B**. Derivatisatie via S_NAr

Product	R_1	R_2	R_3R_3'	Rendement
bf	Bn	Me	$(CH_3CH_2)_2$	18%
bg	Bn	Me	cyclohexyl	43%
bh	Bn	Me	morfolino	39%
bi	Bn	Me	4-Mepiperazinyl	32%
bj	iBu	Bn	cyclohexyl	39%
bk	iBu	Me	2-fenylethyl	35%
bl	3-indolyl(Boc)methyl	Me	cyclohexyl	41%

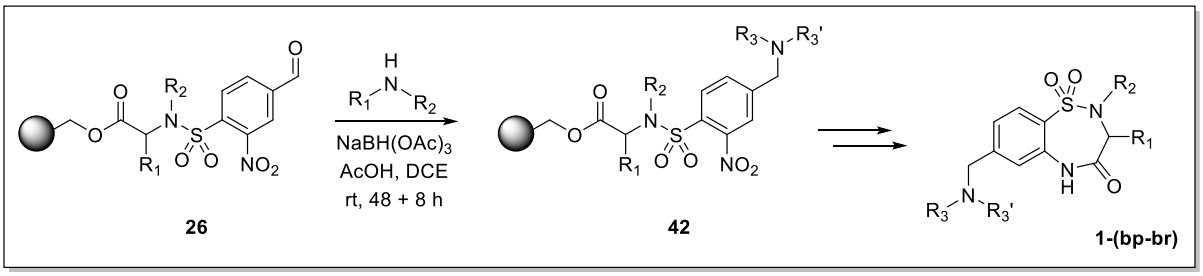
Tabel 11-A Overzicht 8-aminoalkyl-2,3-dihydro-1,2,5-benzothiadiazepin-4(5*H*)-on-1,1-dioxides

Product	R_1	R_2	R_3R_3'	Rendement
bm	Bn	Me	morfolino	12%
bn	Bn	Me	propargyl	7%
bo	Bn	Me	propenyl	10%

Tabel 11-B Overzicht 6-aminoalkyl-2,3-dihydro-1,2,5-benzothiadiazepin-4(5*H*)-on-1,1-dioxides

3.4.3 SYNTHESE VAN 7-ALKYLAMINOMETHYL-2,3-DIHYDRO-1,2,5-BENZOTHIADIAZEPIN-4(5H)-ONE-1,1-DIOXIDES

De laatste bouwsteen die ons toeliet om de benzothiadiazepines te diversifiëren, was 4-formyl-2-nitrobenzeensulfonylchloride **11-g**. Via een reductieve amineringsreactie, door gebruik te maken van $NaBH(OAc)_3$ en een amine in licht zuur midden, kon een alkylaminomethylgroep worden ingebouwd (figuur 11). Zo werden 3 nieuwe benzothiadiazepines bekomen, weergegeven in tabel **12**.



Figuur 11. Derivatisatie via reductieve aminering

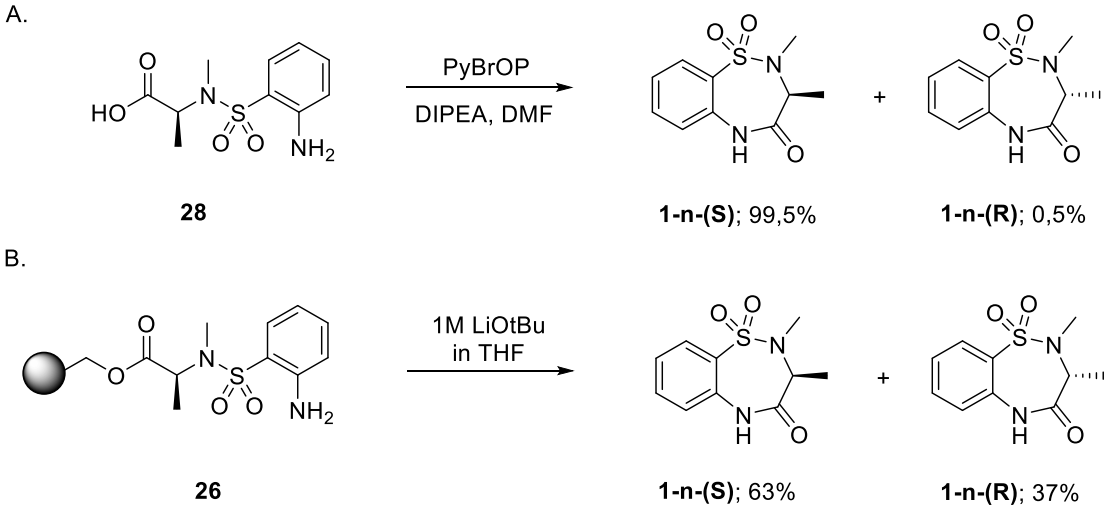
Product	R_1	R_2	R_3R_3'	Rendement
bp	Bn	Me	HBn	13%
bq	Bn	Me	morfolino	20%
br	Bn	Me	4-Mepiperazinyl	22%

Tabel 12. Overzicht van de 2,3-dihydro-7-alkylaminomethyl-1,2,5-benzothiadiazepin-4(5*H*)-on-1,1-dioxides **1-(bp-br)**

3.5 OPTISCHE ZUIVERHEID VAN DE 2,3-DIHYDRO-1,2,5-BENZOTHIADIAZEPIN-4(5H)-ON-1,1-DIOXIDES

Na de optimalisatie van de reactiecondities via de "cyclization/release"-strategie, werd de optische zuiverheid van onze eindmoleculen bekeken. Een analyse via chirale HPLC wees uit dat de eindproducten als een quasi racemisch mengsel van beide enantiomeren voorkwamen, onafhankelijk of zij ringgesloten werden in basische of zuur midden. Hoewel dit een voordeel was voor de uiteindelijke farmaceutische screening, was er toch nood aan een methode voor de synthese van een enantiomeer zuiver product.

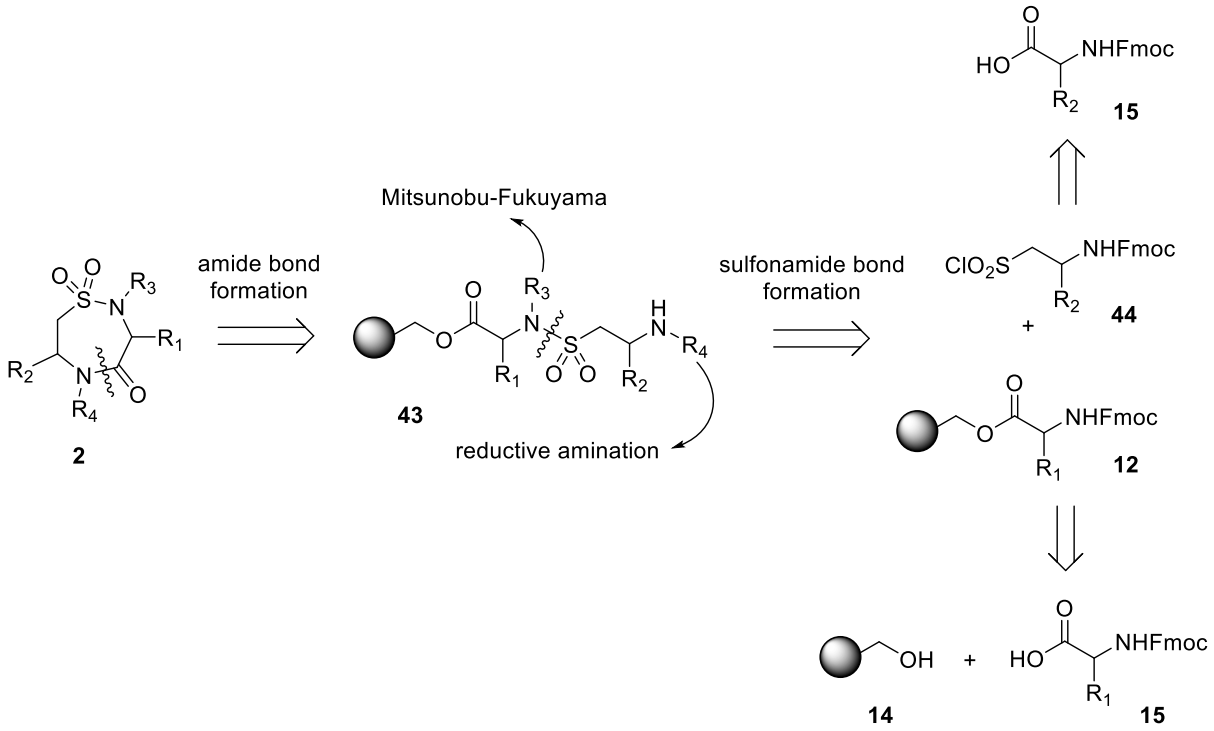
Het verkorten van de reactietijden had geen positief effect op de *ee* alsook een negatief effect op de rendementen en bood dus geen oplossing. Daarop werd opnieuw gekozen voor de synthesestrategie waarbij de ringsluitingsprecursor werd afgesplitst en de ringsluiting vervolgens in oplossing plaatsvond. Deze methode werd getest voor benzothiadiazepine X en gaf een uitstekend resultaat, met een *ee* van ongeveer 99%.



Figuur 12. Overzicht van de graad van racemisatie bij **A.** de ringsluiting in oplossing **B.** de "cyclization/release"-strategie

3.6 SYNTHESE VAN DE 1,2,5-THIADIAZEPAN-4-ON-1,1-DIOXIDES

De tweede doelmolecule van het originele projectvoorstel bestond uit de 1,2,5-thiadiazepan-4-on-1,1-dioxides **2**. Ook voor deze synthese werd geopteerd om eerst de "cyclization/release"-strategie toe passen en de "on-resin"-strategie als alternatief achter de hand te houden, moest de finale ringsluiting problemen opleveren. De synthesestrategie om deze molecule op te bouwen is gelijklopend met deze van de benzothiadiazepines, het grootste verschil ligt hem in het gebruik van een ander type bouwsteen namelijk □-aminoethaansulfonylchlorides in plaats van 2-nitrobenzeensulfonylchlorides (figuur 13).

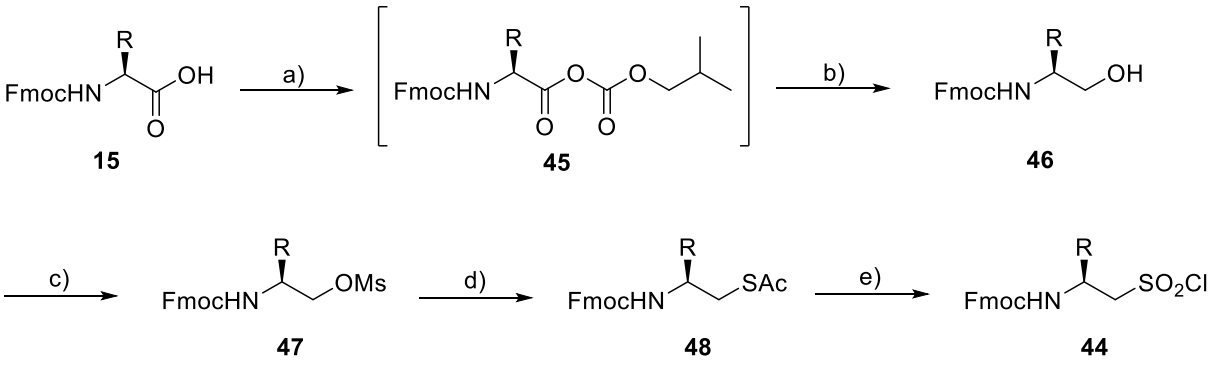


Figuur 13. Retrosyntheseschema van de 1,2,5-thiadiazepan-4-on-1,1-dioxides via de "cyclization/release"-strategie

3.6.1 SYNTHESE VAN β-AMINOETHAANSULFONYLCHLORIDES

De synthese van de thiadiazepanen vereist β-aminoethaansulfonylchlorides **35** als bouwstenen. Een route om tot deze bouwstenen te komen, uitgaande van commercieel verkrijgbare Fmoc-beschermde α-aminozuren, werd reeds in de literatuur beschreven[255] (figuur 14). Deze synthese werd uitgevoerd uitgaande van de aminozuren glycine, alanine en phenylalanine tot vorming van hun respectievelijke β-aminoethaansulfonzuren **35-(a-c)**. De rendementen van elke stap worden voorgesteld in tabel 23.

[255] Brouwer, A. J.; Monnee, M. C. F.; Liskamp, R.M. J. *Synthesis* **2000**, *11*, 1579-1584



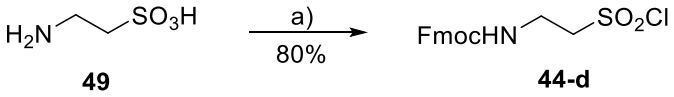
a) iBuOCOCl, NMM, DME, -10°C, 1 min b) $NaBH_4$, H_2O, -10°C, 1 min c) MsCl, Et_3N, CH_2Cl_2, 0°C, 2 h d) HSAc, Cs_2CO_3, DMF, RT, 16 h e) i. H_2O_2, HOAc, RT, 16 h ii. $COCl_2$ (20% v/v in toluene), DMF, CH_2Cl_2, RT, 2 h

Figuur 14. Syntheseroute β-aminoethaansulfonylchlorides **35**

Product	R	46	47	48	44
a	Me	94%	80%	62%	71%
b	Bn	96%	86%	56%	81%
c	O*t*Bu	75%	99%	77%	67%

Tabel 23. Overzicht rendementen synthese β-aminoethaansulfonylchlorides **44**

Om sneller tot een bruikbare bouwsteen te komen, werd ook een synthese opgesteld uitgaande van taurine (figuur 15). Na Fmoc bescherming van de aminefunctie werd direct het sulfonaatzout gevormd, dat na reactie met fosgeen in tolueen direct aanleiding gaf tot het gewenste sulfonylchloride **44-d**.

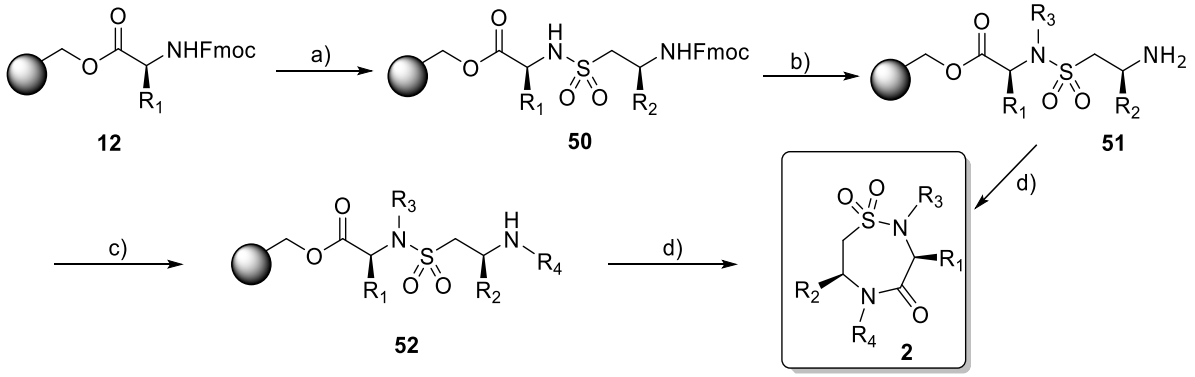


a) i. Fmoc-Cl, H_2O, pH 8-9, CH_3CN ii. $COCl_2$ (20% v/v in toluene), DMF, CH_2Cl_2, rt

Figuur 15. Synthese β-aminoethaansulfonylchloride **44-d** uit taurine

3.6.2 SYNTHESE VAN DE 1,2,5-THIADIAZEPAN-4-ON-1,1-DIOXIDES

De synthese van de thiadiazepanes verliep zoals hieronder weergegeven (figuur 16). Na optimalisatie van de verschillende reactiestappen konden, door gebruik te maken van verschillende α-aminozuren **15**, β-aminoethaansulfonylchlorides **44** en alcoholen, zestien thiadiazepines gesynthetiseerd worden, gevarieerd op drie 3 punten (tabel 24-A). Op de N5 positie kon ook een vierde substituent ingevoerd worden, maar werd er opnieuw gevreesd voor een moeilijke ringsluiting, naar analogie met de benzothiadiazepines. De cyclization/release-reactie gaf in dit geval echter geen problemen, wat resulteerde in negen thiadiazepanen gediversifieerd op 4 posities (tabel 24-B).



a) i. 20% 4-Me-piperidine in DMF, rt ii. **44**, collidine, DMAP, CH_2Cl_2, rt iii. 20% b) i. R_3OH, DIAD, PPh_3, DCE, rt ii. 20% 4-Me-piperidine in DMF, rt c) i. *o*-NsCl, collidine, CH_2Cl_2 ii. R_4OH, DIAD, PPh_3, DCE iii. β-mercaptoethanol, DBU, DMF d) AcOH, THF, 50°C

Figuur 16. Overzicht synthese 1,2,5-thiadiazepan-4-on-1,1-dioxides **2**

Product	R_1	R_2	R_3	Rendement
a	H	H	Me	50%
b	Bn	H	Me	44%
c	5-imidazolyl(Trt)methyl	H	Me	41%
d	3-indolyl(Boc)methyl	H	Me	16%
e	H	CH_2O(tBu)	Me	49%
f	Bn	CH_2O(tBu)	Me	42%
g	3-indolyl(Boc)methyl	CH_2O(tBu)	Me	20%
h	H	Bn	Me	92%
i	H	Bn	Bn	47%
j	iBu	Bn	Me	48%
k	Bn	Me	bifenylmethyl	17%
l	iBu	Me	Me	70%
m	Bn	Me	Me	60%
n	$(CH_2)_2$COO(tBu)	Me	Me	68%
o	H	Me	Me	48%
p	iBu	Bn	Bn	77%

Tabel 24-A. Overzicht 1,2,5-thiadiazepan-4-on-1,1-dioxides **2** op 3 posities

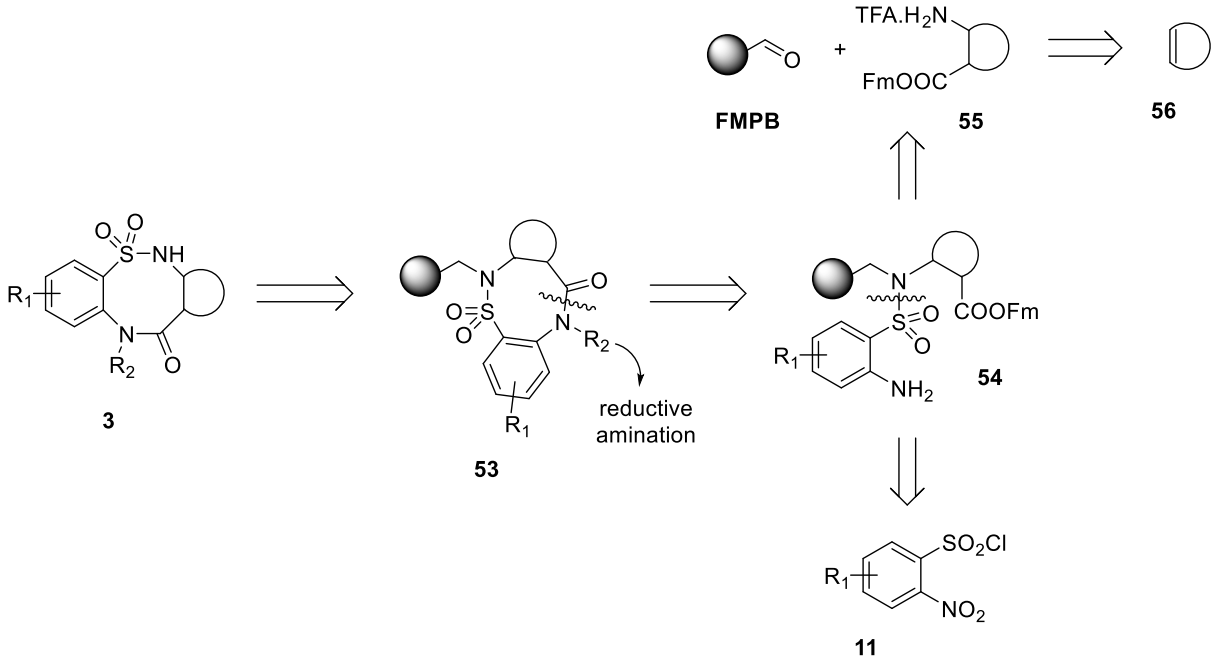
Product	R_1	R_2	R_3	R_4	Rendement
q	$(CH_2)_2$COO(tBu)	H	Me	Me	38%
r	H	H	Me	Me	22%
s	iBu	H	Me	bifenylmethyl	9%
t	iBu	H	Me	2-(N-morpholino)-Et	18%
u	Bn	H	Me	Me	30%
v	H	Bn	Me	Me	41%
w	Bn	H	Me	bifenylmethyl	12%
x	H	Bn	Me	Bn	10%
y	iBu	Bn	Me	Me	3%

Tabel 24-B. Overzicht 1,2,5-thiadiazepan-4-on-1,1-dioxides **2** op 4 posities

3.7 SYNTHESE VAN DE 3,4-DIHYDRO-2*H*-1,2,6-BENZOTHIADIAZOCIN-5(6*H*)-ON-1,1-DIOXIDES

3.7.1 RETROSYNTHETISCH OVERZICHT

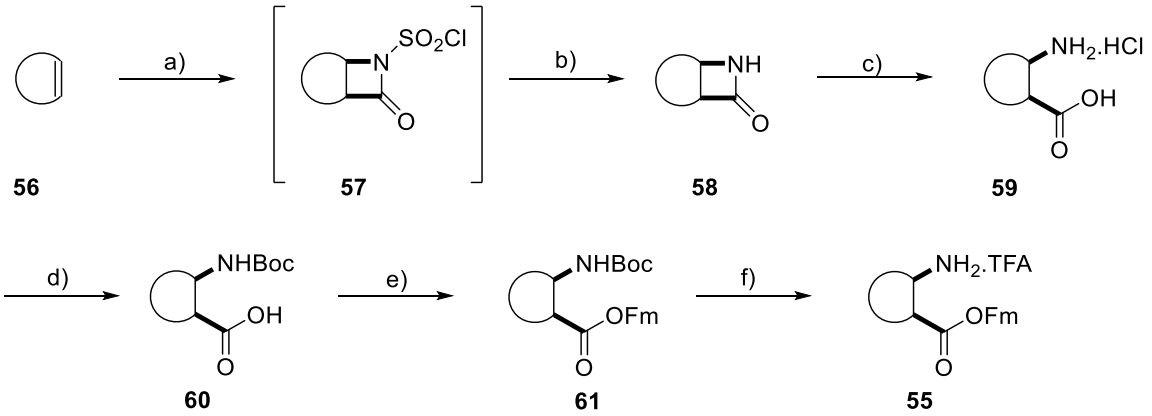
De laatste doelstructuur die tijdens dit project kon behandeld worden, bestond uit de achtringanalogen van de benzothiadiazepines, namelijk de benzothiadiazocines **3**. Om deze structuren op te bouwen werd in plaats van een α-aminozuur een cyclisch β-aminozuur **55** gebruikt, die konden gesynthetiseerd worden uitgaande van hun overeenkomstige cycloalkenen. Als synthesestrategie werd geopteerd voor de "on-resin"-ringsluiting, aangezien een moeilijke lactamvorming verwacht werd.



Figuur 17. Retrosynthetisch overzicht van de "on-resin"-strategie voor de synthese van 3,4-dihydro-2*H*-1,2,6-benzothiadiazocin-5(6*H*)-on-1,1-dioxides

3.7.2 SYNTHESE VAN DE ALICYCLISCHE β-AMINOZUREN

Via een vijfstapssequentie, zoals weergegeven in onderstaand schema, konden de N-Fmoc-beschermde alicylcische *cis*-β-aminozuren **55** worden gesynthetiseerd. In ons geval werden op deze wijze 2 modelbouwsten bereid startende van cyclopenteen en cyclohexaan, waarvan de rendementen van elke synthestap zijn samengevat in tabel 28.



a) i. CSI, CH_2Cl_2, 0°C, 1 h ii. RT, 16h - 48h b) NaI, $NaHSO_3$, H_2O, RT c) 12M HCl, 90°C, 1 h d) Boc_2O, K_2CO_3, dioxane/water 2/1, RT, 16 h e) FmOH, DCC, DMAP, CH_2Cl_2, 0°C, 6 h f) 25% TFA in CH_2Cl_2, RT, 1 h

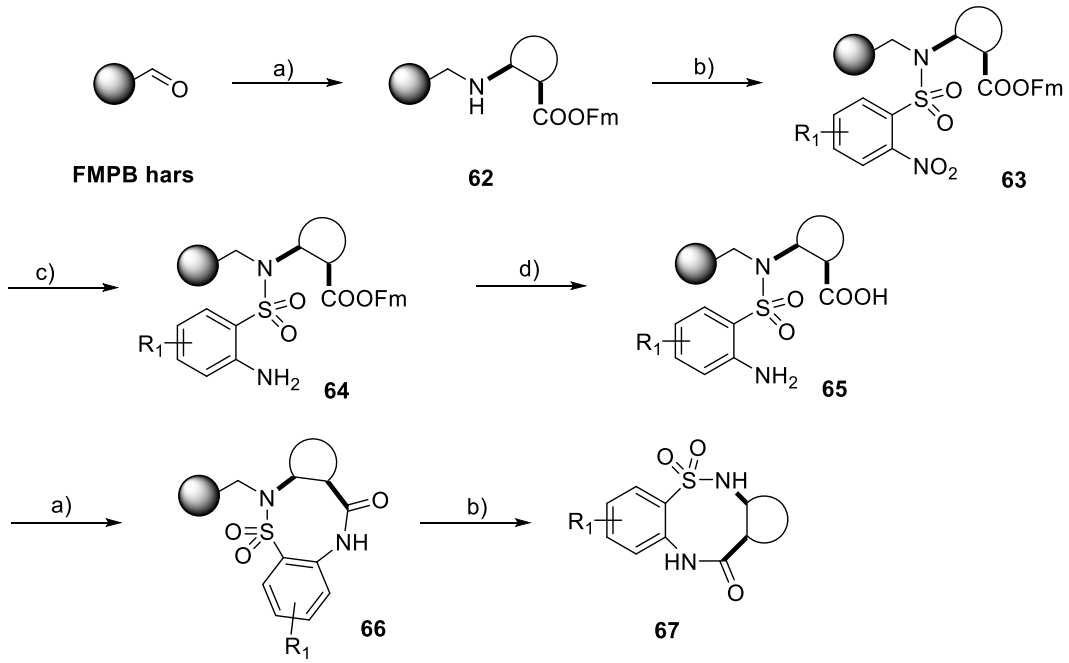
Figuur 18. Synthese alicyclische *cis*-β-aminozuren **55**

Product	56	58	59	60	61	55
a	cyclopenteen	72%	64%	84%	79%	89%
b	cyclohexeen	55%	93%	71%	87%	92%

Tabel 28. Overzicht rendementen voor de synthese van de alicyclische *cis*-β-aminozuren

3.7.3 SYNTHESE 3,4-DIHYDRO-2H-1,2,6-BENZOTHIADIAZOCIN-5(6H)-ON-1,1-DIOXIDES

Eens de synthese van de bouwstenen was afgerond, werd begonnen aan de vastefasesynthese van de doelmoleculen. Uiteindelijk werden na zes synthesestappen, de gewenste eindproducten bekomen (figuur 19). Wegens tijdsgebrek konden van dit type structuren slechts 3 voorbeelden bereid worden in lage rendementen. Waarschijnlijk zijn deze lage rendementen te wijten aan een slechte afsplitsing van de eindmoleculen van de vaste drager, maar verder onderzoek moet dit uitwijzen.



a) i. **55**, $NaBH(OAc)_3$, DCE/DMF 9/1, RT, 16 h ii. 10% DIPEA in CH_2Cl_2, RT, 1 h b) **11**, *sym*-collidine, CH_2Cl_2, RT, 2x 1 h c) $CrCl_2$, DMF/MeOH 9/1, RT, 2x 1 h d) i. 20% 4-Mepiperidine in DMF, RT, 2x 10 min ii. 10% HOAc in CH_2Cl_2, RT, 2x 1 h e) PyBrOP, DIPEA, DMF, RT, 16 h f) 95% TFA in H_2O, RT, 3 h

Figuur 19. Synthese van 3,4-dihydro-2*H*-benzothiadiazocin-5(6*H*)-on-1,1-dioxides via de "on-resin"-strategie

Product	β-aminozuur	R_1	Rendement
a	ACPC	H	7%
b	ACHC	H	7%
c	ACHC	Cl	4%

Tabel 29. Overzicht rendementen 3,4-dihydro-2*H*-benzothiadiazocin-5(6*H*)-on-1,1-dioxides

4 BESLUIT

Het initiële doel van dit project was de synthese van 4 farmaceutische interessante doelmoleculen, gebaseerd op het idee van de zogenaamde *privileged structures*. Om deze doelstructuren te bekomen zou gebruik gemaakt worden van een vastefasesynhtese, die eens geoptimaliseerd, vrij snel zou kunnen leiden tot modelbibliotheken met een grote structurele diversiteit. Voor de 4 doelmoleculen werden 2 alternatieve vastefasestrategieën ontwikkeld, enerzijds een cyclization/release strategie en anderzijds een "on-resin" -strategie, beiden met hun intrinsieke voor- en nadelen.

De eerste doelmolecule die werd onderzocht was 1,2,5-benzothiadiazepin-4(5*H*)-on-1,1-dioxide. Een essentiële bouwsteen voor de opbouw van dit type scaffold waren de 2-nitrobenzeensulfonylchlorides **11**, die niet commercieel beschikbaar waren. Een korte synthese over 3 stappen uitgaande van 2-nitrofenolen, liet ons echter toe acht 2-nitrobenzeensulfonylchlorides te bereiden. Eens deze bouwstenen voorhanden waren, kon een kleine bibliotheek van vierendertig 1,2,5-benzothiadiazepin-4(5H)-on-1,1-dioxides **1**, gevarieerd op 3 posities, worden bereid via een cyclization/release-strategie.

Na de introductie van een vierde substituent op de N5 positie, ontstonden er echter problemen bij de ringsluiting. Daarom werd op de alternatieve syntheseroute, de "on-resin"-strategie, overgeschakeld. Hoewel deze methode aanleiding gaf tot de gewenste producten, waren de rendementen bijzonder laag. Daarop werd besloten om deze moleculen te ringsluiten in oplossing, na afsplitsen van de vaste drager. Via deze methode werden vier N5-gealkyleerde benzothiadiazpines bekomen.

De introductie van gefunctionaliseerde 2-nitrobenzeensulfonylchlorides **11** liet toe om onze doelmoleculen nog verder te derivatiseren. Zo werden door toepassen van een Suzuki cross-coupling, een nucleofiel aromatische substitutie en een reductieve aminering in totaal 26 extra benzothiadiazepines aan onze bibliotheek toegevoegd.

Het toepassen van de basische en zure condities tijdens de ringsluiting hadden als gevolg dat de benzothiadiazepines gesynthetiseerd werden als hun racematen. Om enantiomeer zuivere benzothiadiazepines te bekomen, werd de methode om tot de N5 gealkyleerde benzothiadiazepines, namelijk afsplitsen en ringsluiten in oplossing, toegepast. Deze methode leidde succesvol tot een enantiomeer zuiver product.

Vervolgens werd met de synthese van de 1,2,5-thiadiazepan-4-on-1,1-dioxides **2** gestart. Om tot deze doelmoleculen te komen moesten eerst de nodige b-aminoethaansulfonylchlorides gesynthetiseerd worden, essentiële bouwstenen voor dit type structuur. Deze konden via een literatuurprocedure bereid worden uitgaande van α-aminozuren in 5 stappen en leidden uiteindelijk tot 3 bouwstenen. Vanuit taurine kon op een voudige wijze een vierde bouwsteen worden toegevoegd. Via de "cyclization/release"-strategie konden vervolgens vlot de synthesestappen op vastefase worden uitgevoerd, wat uiteindelijk leidde tot de zeventien 1,2,5-thiadiazepan-4-on-1,1-dioxides, gevarieerd op 3 posities. Het invoeren van een vierde substituent op de N5 positie verliep vlot, alsook de aansluitende ringsluiting. Op deze wijze werden nog negen thiadiazepanen aan onze bibliotheek toegevoegd, gevarieerd op 4 posities.

Als laatste doelmolecule werden de 3,4-dihydro-2*H*-1,2,6-benzothiadiazocin-5(6*H*)-on-1,1-dioxides **3** behandeld. Voor dit type structuren werden ook eerst de nodige bouwstenen bereid, namelijk alicyclische β-aminozuren, en dit uitgaande van hun overeenkomstige cycloalkenen. Na de succesvolle synthese van twee van deze bouwstenen, werd getracht de thiadiazocines te bereiden via de "on-resin"-strategie. Uiteindelijk konden ook hier drie doelmoleculen bereid worden, hetzij met lage rendementen. Verder onderzoek is voor deze synthese dan ook nog vereist.

CHAPTER V: EXPERIMENTAL PROCEDURES

1 INSTRUMENTATION AND METHODS

1.1 SOLVENTS AND REAGENTS

All commercial solvents and reagents were used as received, unless otherwise noted. Reactions in solution were performed with solvents of technical quality, reactions on solid phase were performed with dry solvents of HPLC quality. Washing of the resins was performed with solvents of technical grade. Dichloromethane, 1,2-dichloroethane, pyridine, triethylamine and diisopropylethylamine were dried on calcium chloride. DMF was dried and stored on molecular sieves of 4Å. THF was dried on sodium and benzophenone.

1.2 PURIFICATION

Column chromatography was performed standard with Grace Division LC 60Å silica (60-200 μm) or in some cases with Rocc silica 60Å (40-60 μm). The eluent consisted of technical solvents for large scale purification and of HPLC solvents for small scale purifications.

Preparative HPLC-purifications of more than 10 mg crude product were performed on a Phenomenex Luna C18 column (5μm, 250 x 21,20 mm), making use of a Kontron 422 type HPLC-pump and a MELZ lcd 312 RI-detector. For purifications of less than 10 mg product, an adjusted Phenomenex Luna C18 column (5μm, 250 x 10,00 mm) was applied on the same system.

1.3 CHARACTERIZATION

Reactions in solution were followed using Thin Layer Chromatography (TLC). The R_f values were determined on Machery-Nagel SIL-G25 U254 TLC-plates, by using UV-light (254 nm) or by developing them with a suitable staining reagent (a $KMnO_4$ solution in water or cerium molybdate/Hanessian's staining).

Reactions on solid phase were monitored by LC-MS, cleaving off a small amount of product from the solid support by treatment with an appropriate cleavage reagent. The analyses were performed on the VL type Agilent 1100 LC/MS system, charged with a Phenomenex Luna C18 column (methods A and B) or with a Kinetex C18 column (methods C and D). A 5mM solution of NH_4OAc in water (solvent A) and acetonitrile (solvent B) were used as eluents on this system. The gradients are mentioned below.

Method A:

time	solvent A	solvent B
0-2 min	100	0
2 min	100	0
17 min	0	100
17-22 min	0	100

Method B:

time	solvent A	solvent B
0-2 min	75	0
2 min	75	0
17 min	0	100
17-22 min	0	100

Method C:

time	solvent A	solvent B
0-1 min	100	0
1 min	100	0
7 min	0	100
7-9 min	0	100

Method D:

time	solvent A	solvent B
0-1 min	75	0
1 min	75	0
7 min	0	100
7-9 min	0	100

Optical rotations were measured on a Perkin Elmer 214 polarimeter at 589 nm (sodium lamp). UV spectra were recorded using a Hitachi U-2010 UV-VIS Spectrofotometer. NMR analyses were performed on a Bruker Avance 300, a Bruker DRX500 or Bruker Avance II 700. ^{1}H NMR measurements were performed at 300, 500 or 700 MHz, ^{13}C NMR measurements at 75 or 125 MHz on the aforementioned spectrometers. Chemical shifts are reported in ppm, using the residual solvent signal as reference value ($CDCl_3$: 7,26 ppm/77 ppm, CD_2Cl: 5,32 ppm/54 ppm, DMSO-d6: 2,50 ppm/39,51 ppm)

1.4 EQUIPMENT

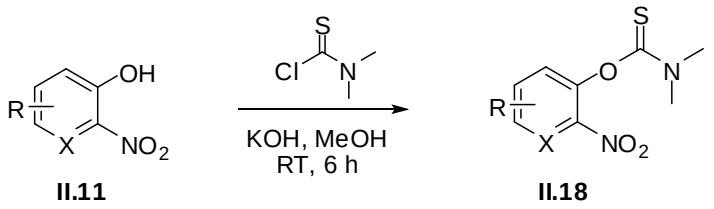
Microwave reactions were performed on a CEM Discover Focused Microwave Synthesis System in closed vessel glass tubes.

Solid phase reactions were performed on a Bohdan MiniBlock High Capacity Shaking and Washing Station. Small scale solid phase reactions (< 50 mg resin) were performed in small glass vials using a Selecta Vibromatic whristshaker. Large scale reactions (> 20 ml of solvent required) were performed in homemade glass tubes equipped with a glass fritted filter and filtration system for the vacuum pump.

2 SYNTHESIS OF SUBSTITUTED 2-NITROBENZENESULFONYL CHLORIDES

2.1 SYNTHESIS OF THE O-THIOCARBAMATES

2.1.1 GENERAL PROCEDURE FOR O-THIOCARBAMATES **II.18-(A-F,H)**



II.11 **II.18**

X = C: **II.11-(a-g)**
X = N: **II.11-h**

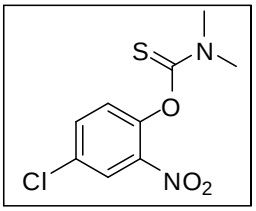
KOH (11.5 mmol, 2 eq) is added to a flask filled with 25 ml of methanol and stirred until all the KOH is soluted. Subsequently, 2-nitrophenol **II.11-(a-h)** (5.76 mmol, 1 eq) is added to this solution and stirring is continued for 5 min (the reaction mixture becomes an intensily red solution). After 5 min, N,N-dimethylthiocarbamoyl chloride (11.5 mmol, 2 eq) is added portionwise to the reaction mixture, turning the solution in a turbid yellowish suspension. This mixture is stirred further for 3-6h, depending on the substrate, before it is quenched with 100 ml water. The precipitated product is then filtered off, thoroughly washed with water and desiccated on the freeze-dryer. No further purification is needed for these O-thiocarbamates **II.18-(a-c, g)**.

An alternative work-up procedure is applied for products that did not precipitate when quenched with water i.e. **II.18-(d-f, h)**:

After 3 h stirring, half of the methanol from the reaction mixture is evaporated under reduced pressure. After adding 100 ml of water, this crude mixture is extracted 3 times with 80 ml of EtOAc. The collected organic phases are subsequently washed 1 time with 150 ml 5% Na_2CO_3 solution and 1 time with 150 ml brine, dried on $MgSO_4$, filtered off and evaporated under reduce pressure to yield the desired O-thiocarbamates **II.18-(d-f, h)**. Purification is done by flash chromatography with an eluent depending on the substrate and described for each compound individually hereunder.

In the case of 4-formyl-2-nitrophenol **II.11-f**, the dimethylacetal was formed during reaction. This acetal was first purified using column chromatography and then transformed to the aldehyde again by stirring it in a 2% solution of HCl in dioxane/water 50/50. Extraction of the resulting suspension 3x with CH_2Cl_2, drying the collected organic phases over $MgSO_4$ and evaporating the solvents under reduced pressure, readily yielded the desired product **II.18-f** as a pale yellow solid in 83% yield.

2.1.2 O-(4-CHLORO-2-NITROPHENYL)DIMETHYLCARBAMOTHIOATE **II.18-A**



Yield: 92% (brownish crystals)

Formula: $C_9H_9ClN_2O_3S$

Molecular weight: 260,70 g/mol

LC-MS:

t_{ret} = 17,3 min (Method A)
ES-MS [m/z (fragment, intensity)]: 261,0 ($M+H^+$,100)

HR-MS (ESI): calculated for [$M+H^+$] = 261,0101, found 261,0094

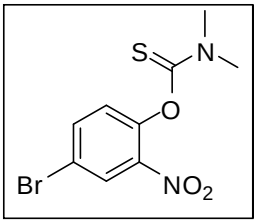
^{1}H NMR: (300 MHz, CHLOROFORM-d) δ ppm 8.11 (d, *J*=2.4 Hz, 1 H) 7.62 (dd, *J*=8.7, 2.6 Hz, 1 H) 7.21 (d, *J*=8.7 Hz, 1 H) 3.45 (s, 3 H) 3.39 (s, 3 H)

^{13}C NMR: (75 MHz, CHLOROFORM-*d*) δ 185.56 (C) 145.81 (C) 134.33 (CH) 131.94 (C) 127.84 (CH) 125.70 (CH) 43.60 (CH_3) 39.14 (CH_3) ppm (quaternary carbon on position 2 not visible)

IR (HATR): 3079 (vw) 3060 (vw) 2933 (vw) 2879 (vw) 1535 (s) 1476 (m) 1413 (w) 1399 (m) 1352 (m) 1282 (m) 1252 (m) 1225 (m) 1175 (w) 1150 (w) 1113 (m) 1101 (m) 901 (w) 890 (w) 834 (w) 761 (w) 734 (m)

TLC: R_f = 0,23 (hexane/EtOAc 80/20)

2.1.3 O-(4-BROMO-2-NITROPHENYL)DIMETHYLCARBAMOTHIOATE **II.18-B**



Yield: 97% (yellow solid)

Formula: $C_9H_9BrN_2O_3S$

Molecular weight: 305,15 g/mol

LC-MS:

t_{ret} = 17,7 min (Method A)
ES-MS [m/z (fragment, intensity)]: 304,9 ($M(^{79}Br)+H^+$, 50), 306,9 ($M(^{81}Br+H^+$, 50)

HR-MS (ESI): calculated for [$M+H^+$] = 304,9596, found 304,9586

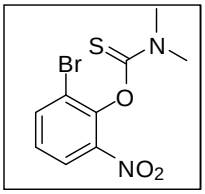
^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 8.25 (d, *J*=2.4 Hz, 1 H) 7.77 (dd, *J*=8.7, 2.4 Hz, 1 H) 7.15 (d, *J*=8.7 Hz, 1 H) 3.46 (s, 3 H) 3.39 (s, 3 H)

^{13}C NMR: (75 MHz, CHLOROFORM-*d*) δ 185,46 (C) 146.33 (C) 137.31 (CH) 128.59 (CH) 128.13 (CH) 119.05 (C) 43.60 (CH_3) 39.15 (CH_3) ppm (quaternary carbon on position 2 not visible)

IR (HATR): 3096 (vw) 2942 (w) 2869 (vw) 1600 (w) 1525 (s) 1473 (m) 1396 (m) 1341 (m) 1282 (m) 1253 (m) 1218 (s) 1170 (m) 1149 (m) 1108 (m) 1091 (s) 880 (m) 825 (m) 758 (w) 718 (m)

TLC: R_f = 0,28 (hexane/EtOAc 80/20)

2.1.4 O-(6-BROMO-2-NITROPHENYL)DIMETHYLCARBAMOTHIOATE **II.18-C**



Yield: 56% (yellow solid)

Formula: $C_9H_9BrN_2O_3S$

Molecular weight: 305,15 g/mol

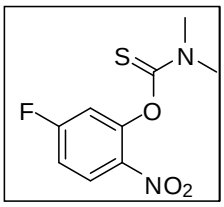
LC-MS:
t_{ret} = 17,0 min (Method A)
ES-MS [m/z (fragment, intensity)]: 304,9 (M(^{79}Br)+H^+, 50), 306,9 (M(^{81}Br)+H^+, 50)

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 8.07 (dd, *J*=8.3, 1.5 Hz, 1 H) 7.89 (dd, *J*=8.0, 1.6 Hz, 1 H) 7.29 (t, *J*=8.2 Hz, 1 H) 3.47 (s, 3 H) 3.44 (s, 3 H)

^{13}C NMR: (75 MHz, CHLOROFORM-*d*) δ 183,99 (C) 144.94 (C) 138.16 (CH) 126.91 (CH) 124.83 (CH) 120.78 (C) 43.69 (CH_3) 39.21 (CH_3) ppm (quaternary carbon on position 2 not visible)

TLC: R_f = 0,21 (hexane/EtOAc 80/20)

2.1.5 O-(5-FLUORO-2-NITROPHENYL)DIMETHYLCARBAMOTHIOATE **II.18-D**



Yield: 94% (yellow solid)

Formula: $C_9H_9FN_2O_3S$

Molecular weight: 244,24 g/mol

LC-MS:
t_{ret} = 16,6 min (Method A)
ES-MS [m/z (fragment, intensity)]: 245,0 (M+H^+, 100)

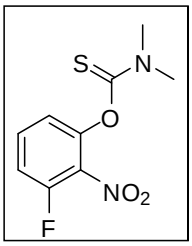
^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 8.19 (dd, *J*=9.1, 5.6 Hz, 1 H) 7.10 (ddd, *J*=9.4, 7.0, 2.6 Hz, 1 H) 6.99 (dd, *J*=8.5, 2.6 Hz, 1 H) 3.46 (s, 23 H) 3.40 (s, 3 H)

^{13}C NMR: (75 MHz, CHLOROFORM-*d*) δ 185,23 (C) 165.11 (d, *J*=259.07Hz, C) 149.15 (d, *J*=12.63 Hz, C) 127.78 (d, *J*=10.98, CH) 114.37 (d, *J*=25.25, CH) 113.75 (d, *J*=23.05, CH) 43.57 (CH_3) 39.18 (CH_3) ppm (quaternary carbon on position 2 not visible)

IR (HATR): 3099 (vw) 3041 (vw) 1612 (w) 1598 (w) 1542 (w) 1520 (w) 1483 (w) 1396 (w) 1344 (w) 1287 (w) 1265 (w) 1233 (w) 1158 (w) 1107 (m) 986 (w) 927 (vw) 877 (w) 838 (w) 750 (w) 735 (w) 704 (w) 672 (vw) 617 (vw)

TLC: R_f = 0,33 (hexane/EtOAc 80/20)

2.1.6 O-(3-FLUORO-2-NITROPHENYL)DIMETHYLCARBAMOTHIOATE **II.18-E**



Eluent: hexane/ethyl acetate 80/20

Yield: 89% (dark yellow solid)

Formula: $C_9H_9FN_2O_3S$

Molecular weight: 244,24 g/mol

LC-MS:
t_{ret} = 16,4 min (Method A)
ES-MS [m/z (fragment, intensity)]: 245,0 ($M+H^+$, 100)

HR-MS (ESI): calculated for [$M+H^+$] = 245,0396, found 245,0389

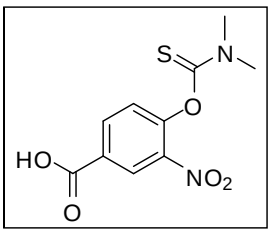
^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 7.53 (td, *J*=8.5, 5.8 Hz, 1 H) 7.18 (td, *J*=8.9, 1.1 Hz, 1 H) 7.10 (dt, *J*=8.4, 1.4 Hz, 1 H) 3.43 (s, 3 H) 3.33 (s, 3 H)

^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ 185,11 (C) 154.73 (d, *J*=260.71, C) 146.65 (C) 131.81 (d,*J*=9.33, CH) 121.58 (d, *J*=3.84, CH) 114.62 (d, *J*=19.76, CH) 43.62 (CH_3) 39.11 (CH_3) ppm (quaternary carbon on position 2 not visible)

IR (HATR): 3083 (vw) 2950 (vw) 2355 (w) 1604 (m) 1531 (m) 1472 (m) 1393 (m) 1357 (m) 1295 (w) 1266 (m) 1238 (m) 1164 (m) 1108 (m) 1058 (w) 1030 (m) 928 (w) 895 (w) 855 (w) 797 (w) 751 (w) 700 (w) 685 (w)

TLC: R_f = 0,53 (pentane/EtOAc 60/40)

2.1.7 4-(DIMETHYLTHIOCARBAMOYL)-3-NITROBENZOIC ACID **II.18-F**



Yield: 29% (crude)

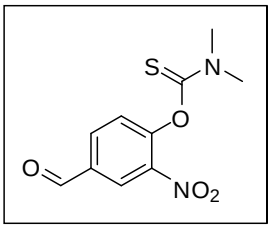
Formula: $C_{10}H_{10}N_2O_5S$

Molecular weight: 270,26 g/mol

LC-MS:
t_{ret} = 10,9 min (Method A)
ES-MS [m/z (fragment, intensity)]: 269,0 ($M-H^+$, 70), 224,9 ($M-H^+-CO_2$, 30)

TLC: R_f = 0,02 (hexane/EtOAc 80/20)

2.1.8 O-(4-FORMYL-2-NITROPHENYL)DIMETHYLCARBAMOTHIOATE **II.18-G**



Eluent: hexane/ethyl acetate 90/10 (dimethylacetal)

Yield: 83% (yellow solid)

Formula: $C_{10}H_{10}N_2O_4S$

Molecular weight: 254,26 g/mol

LC-MS:
t_{ret} = 14,9 min (Method A)
ES-MS [m/z (fragment, intensity)]: 255,1 ($M+H^+$, 50), 277,0 ($M+Na^+$, 50)

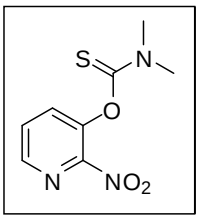
^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 10.07 (s, 1 H) 8.42 (d, *J*=1.7 Hz, 1 H) 8.05 (dd, *J*=8.1, 1.7 Hz, 1 H) 7.93 (d, *J*=8.1 Hz, 1 H) 2.84 - 3.28 (m, 6 H)

^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ 189.14 (CHO) 188,71 (C) 134.24 (C) 134.07 (CH) 127.78 (CH) 127.19 (CH) 125.00 (C) 43.58 (CH_3) 39.30 (CH_3) ppm (quaternary carbon on position 2 not visible)

IR (HATR): 3071 (vw) 2933 (w) 2852 (w) 1699 (m) 1671 (m) 1601 (m) 1533 (m) 1473 (w) 1402 (w) 1357 (m) 1291 (w) 1255 (w) 1230 (m) 1197 (m) 1096 (m) 1047 (m) 945 (w) 920 (w) 902 (w) 818 (w) 756 (w) 727 (w) 683 (w) 652 (w)

TLC: R_f = 0,35 (hexane/EtOAc 60/40), R_f dimethylacetal = 0,45 (hexane/EtOAc 60/40)

2.1.9 O-(2-NITROPYRIDIN-3-YL)DIMETHYLCARBAMOTHIOATE **II.18-H**



Yield: 76% (pink solid)

Formula: $C_8H_9N_3O_3S$

Molecular weight: 227,24 g/mol

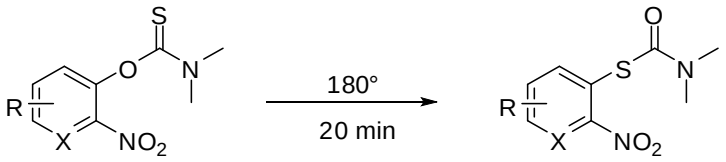
LC-MS:
t_{ret} = 14,7 min (Method A)
ES-MS [m/z (fragment, intensity)]: 228,0 ($M+H^+$, 100)

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 8.46 (dd, *J*=4.5, 1.5 Hz, 1 H) 7.76 (dd, *J*=8.1, 1.5 Hz, 1 H) 7.68 (dd, *J*=8.1, 4.5 Hz, 1 H) 3.44 - 3.48 (m, 3 H) 3.36 - 3.41 (m, 3 H)

^{13}C NMR: (75 MHz, CHLOROFORM-*d*) δ 185,00 (C) 145.20 (CH) 143.09 (C) 136.62 (CH) 129.08 (CH) 43.64 (CH_3) 39.18 (CH_3) ppm (quaternary carbon on position 2 not visible)

TLC: R_f = 0,38 (hexane/EtOAc 70/30)

2.2 SYNTHESIS OF S-THIOCARBAMATES



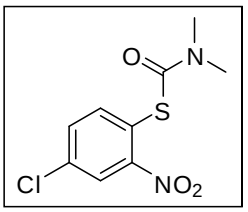
II.18 **II.19**

X = C: **II.18-(a-g)**
X = N: **II.18-h**

2.2.1 GENERAL PROCEDURE

The O-thiocarbamate **II.18** is brought into a flask and equipped with a reflux cooler and stirring bar. The solid is heated up to 180°C, melting it into a brownish liquid. This liquid is subsequently stirred for another 20 min and then allowed to cool down. The brown, glaslike solid is then, if necessary, purified using flash chromatography with an appropriate eluent, delivering the pure S-thiocarbamate **II.19**.

2.2.2 S-(4-CHLORO-2-NITROPHENYL)DIMETHYLCARBAMOTHIOATE **II.19-A**



Yield: 99% (brown solid)

Formula: $C_9H_9ClN_2O_3S$

Molecular weight: 260,70 g/mol

LC-MS:

t_{ret} = 16,6 min (Method A)
ES-MS [m/z (fragment, intensity)]: 261,0 ($M+H^+$, 80), 282,9 ($M+Na^+$, 20)

HR-MS (ESI): calculated for [$M+H^+$] = 261,0101, found 261,0092

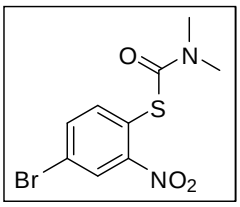
^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 7.93 (d, *J*=2.3 Hz, 1 H) 7.64 (d, *J*=8.5 Hz, 1 H) 7.55 (dd, *J*=8.5, 2.3 Hz, 1 H) 2.92 - 3.22 (m, 6 H)

^{13}C NMR: (75 MHz, CHLOROFORM-*d*) δ 163.83 (C) 139.05 (CH) 135.90 (C) 132.30 (CH) 125.02 (CH) 122.97 (C) 37.17 (CH_3) ppm (quaternary carbon on position 2 not visible)

IR (HATR): 3085 (w) 3011 (vw) 2934 (w) 1667 (s) 1632 (w) 1586 (w) 1558 (w) 1530 (s) 1462 (m) 1443 (w) 1412 (w) 1355 (s) 1307 (w) 1261 (m) 1155 (w) 1130 (w) 1096 (s) 1064 (m) 1048 (m) 910 (w) 890 (m) 882 (m) 831 (m) 768 (m) 754 (w) 698 (w) 685 (w) 660 (w) 651 (w)

TLC: R_f = 0,14 (hexane/EtOAc 80/20)

2.2.3 S-(4-BROMO-2-NITROPHENYL)DIMETHYLCARBAMOTHIOATE **II.19-B**



Yield: 97% (brown solid)

Formula: $C_9H_9BrN_2O_3S$

Molecular weight: 305,15 g/mol

LC-MS:

t_{ret} = 16,9 min (Method A)
ES-MS [m/z (fragment, intensity)]: 304,9 (M(^{79}Br)+H^+, 50), 307,0 (M(^{81}Br) +H^+, 50)

HR-MS (ESI): calculated for [M+H^+] = 304,9596, found 304,9585

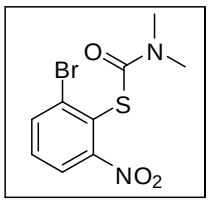
^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 8.07 (d, *J*=2.1 Hz, 1 H) 7.70 (dd, *J*=8.4, 2.2 Hz, 1 H) 7.56 (d, *J*=8.3 Hz, 1 H) 2.95 - 3.17 (m, 6 H)

^{13}C NMR: (75 MHz, CHLOROFORM-*d*) δ 163.69 (C) 139.15 (CH) 135.25 (CH) 127.80 (CH) 123.58 (C) 123.38 (C) 37.14 (CH_3) ppm (quaternary carbon on position 2 not visible)

IR (HATR): 3083 (w) 2933 (w) 1669 (m) 1580 (w) 1555 (w) 1529 (m) 1459 (m) 1408 (w) 1352 (m) 1258 (w) 1153 (w) 1098 (m) 1087 (m) 1048 (w) 904 (w) 890 (w) 873 (w) 829 (w) 753 (m) 684 (w) 651 (w)

TLC: R_f = 0,20 (hexane/EtOAc 80/20)

2.2.4 S-(6-BROMO-2-NITROPHENYL)DIMETHYLCARBAMOTHIOATE **II.19-C**



Yield: 98% (dark green solid)

Formula: $C_9H_9BrN_2O_3S$

Molecular weight: 305,15 g/mol

LC-MS:

t_{ret} = 16,2 min (Method A)
ES-MS [m/z (fragment, intensity)]: 304,9 (M(^{79}Br)+H^+, 85), 306,9 (M(^{81}Br)+H^+, 85), 327,0 (M(^{79}Br)+Na^+, 15), 328,9 (M(^{81}Br)+Na^+, 15)

HR-MS (ESI): calculated for [M+H^+] = 304,9596, found 304,9593

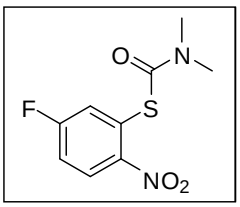
^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 7.90 (dt, *J*=8.1, 0.7 Hz, 1 H) 7.75 (dd, *J*=8.1, 1.1 Hz, 1 H) 7.40 (t, *J*=8.0 Hz, 1 H) 3.08 (d, *J*=31.5 Hz, 6 H) (quaternary carbon on position 2 not visible)

^{13}C NMR: (75 MHz, CHLOROFORM-*d*) δ 162.70 (C) 136.45 (CH) 133.47 (C) 131.00 (CH) 125.26 (C) 123.14 (CH) 37.17 (CH_3) ppm

IR (HATR): 3076 (w) 2929 (w) 1674 (m) 1529 (m) 1480 (w) 1432 (w) 1406 (w) 1359 (m) 1255 (m) 1198 (w) 1137 (w) 1096 (m) 1048 (w) 902 (w) 868 (w) 800 (m) 744 (m) 714 (m) 704 (m) 681 (m) 650 (w)

TLC: R_f = 0,08 (hexane/EtOAc 80/20)

2.2.5 S-(5-FLUORO-2-NITROPHENYL)DIMETHYLCARBAMOTHIOATE **II.19-D**



Yield: 99% (brown solid)

Formula: $C_9H_9FN_2O_3S$

Molecular weight: 244,24 g/mol

LC-MS:

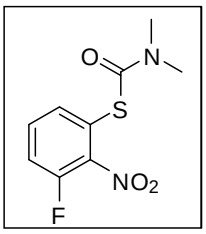
t_{ret} = 15,8 min (Method A)
ES-MS [m/z (fragment, intensity)]: 245,0 ($M+H^+$, 100)

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 8.02 (dd, *J*=9.0, 5.1 Hz, 1 H) 7.48 (dd, *J*=8.5, 2.6 Hz, 1 H) 7.19 (ddd, *J*=9.2, 7.0, 2.6 Hz, 1 H) 3.08 (d, *J*=23.0 Hz, 6 H)

^{13}C NMR: (75 MHz, CHLOROFORM-*d*) δ 165.10 (C) 162.64 (d, J=, C) 128.17 (d, J=0.13, C) 127.18 (d, J=0.13, CH) 124.54 (d, J=33, CH) 116.57 (d, J=31, CH) 37.17 (CH_3) ppm (quaternary carbon on position 2 not visible)

TLC: R_f = 0,22 (hexane/EtOAc 80/20)

2.2.6 S-(3-FLUORO-2-NITROPHENYL)DIMETHYLCARBAMOTHIOATE **II.19-E**



Eluent: hexane/ethyl acetate 80/20

Yield: 95% (yellow solid)

Formula: $C_9H_9FN_2O_3S$

Molecular weight: 244,24 g/mol

LC-MS:
t_{ret} = 16,4 min (Method A)
ES-MS [m/z (fragment, intensity)]: 245,0 ($M+H^+$, 100)

HR-MS (ESI): calculated for [$M+H^+$] = 245,0396, found 245,0391

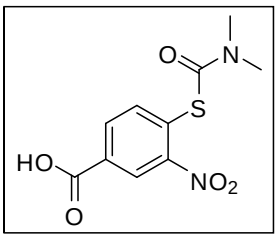
^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 7.43 - 7.56 (m, 2 H) 7.28 - 7.36 (m, 1 H) 3.05 (d, *J*=14.5 Hz, 6 H)

^{13}C NMR: (75 MHz, CHLOROFORM-*d*) δ 153.71 (d, *J*=259.62, C) 133.87 (CH) 131.40 (d, *J*=8.23, CH) 124.23 (d, *J*=8.78, C) 118.43 (d, *J*=19.21, CH) 37.24 (CH_3) 37.08 (CH_3) ppm (quaternary carbon on position 2 not visible)

IR (HATR): 3074 (vw) 2932 (vw) 1677 (m) 1596 (w) 1584 (m) 1540 (m) 1460 (m) 1408 (w) 1362 (m) 1259 (m) 1154 (w) 1096 (m) 1058 (w) 984 (vw) 901 (m) 850 (w) 791 (m) 733 (s) 703 (m) 683 (m) 652 (m)

TLC: R_f = 0,11 (hexane/EtOAc 80/20)

2.2.7 4-S-(DIMETHYLTHIOCARBAMOYL)-3-NITROBENZOIC ACID **II.19-F**



Yield: 95%

Formula: $C_{10}H_{10}N_2O_5S$

Molecular weight: 270,26 g/mol

LC-MS:

t_{ret} = 10,4 min (Method A)

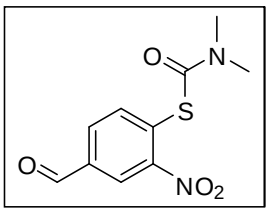
ES-MS [m/z (fragment, intensity)]: 269,0 ($M\text{-}H^+$, 60), 225,0 ($M\text{-}H^+\text{-}CO_2$, 40)

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 8.44 (d, *J*=1.9 Hz, 1 H) 8.19 (dd, *J*=8.1, 1.9 Hz, 1 H) 7.87 (d, *J*=8.1 Hz, 1 H) 3.00 (d, *J*=44.1 Hz, 6 H)

^{13}C NMR: (75 MHz, DMSO-d_6) δ 165.14 (C) 162.08 (C) 151.57 (C) 138.04 (CH) 132.60 (CH) 132.58 (C) 128.50 (C) 125.18 (CH) 36.75 (CH_3) ppm (quaternary carbon on position 2 not visible)

TLC: R_f = 0,01 (hexane/EtOAc 80/20)

2.2.8 S-(4-FORMYL-2-NITROPHENYL)DIMETHYLCARBAMOTHIOATE **II.19-G**



Eluent: from hexane/ethyl acetate 90/10 to hexane/ethyl acetate 50/50

Yield: 95% (yellow product)

Formula: $C_{10}H_{10}N_2O_4S$

Molecular weight: 254,26 g/mol

LC-MS:

t_{ret} = 5,4 min (method C)

ES-MS [m/z (fragment, intensity)]: 253,0 ($M\text{-}H^+$, 70), 182.0 ($M\text{-}H^+\text{-}CON(Me)_2$, 30)

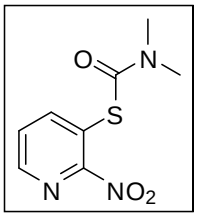
^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 9.83 - 10.25 (m, 1 H) 8.42 (d, *J*=1.7 Hz, 1 H) 8.05 (dd, *J*=8.1, 1.7 Hz, 1 H) 7.93 (d, *J*=7.9 Hz, 1 H) 3.10 (d, *J*=31.3 Hz, 6 H)

^{13}C NMR: (75 MHz, CHLOROFORM-*d*) δ 189.14 (CHO) 163.03 (C=O) 138.30 (CH) 136.56 (C) 132.03 (C) 131.55 (CH) 125.47 (CH) 37.29 (CH_3) ppm (quaternary carbon on position 2 not visible)

IR (HATR): 3054 (vw) 2931 (vw) 1701 (w) 1671 (w) 1600 (vw) 1528 (w) 1348 (w) 1264 (w) 1196 (vw) 1098 (w) 1047 (w) 947 (vw) 906 (w) 819 (vw) 733 (m) 703 (w)

TLC: R_f = 0,35 (hex/EtOAc 60/40)

2.2.9 S-(2-NITROPYRIDIN-3-YL)DIMETHYLCARBAMOTHIOATE **II.19-H**



Yield: 92%

Formula: $C_8H_9N_3O_3S$

Molecular weight: 227,24 g/mol

LC-MS:

t_{ret} = 14,1 min (Method A)

ES-MS [m/z (fragment, intensity)]: 228,0 ($M+H^+$, 50), 250,0 ($M+Na^+$, 50)

HR-MS (ESI): calculated for [$M+H^+$] = 228,0443, found 228,0437

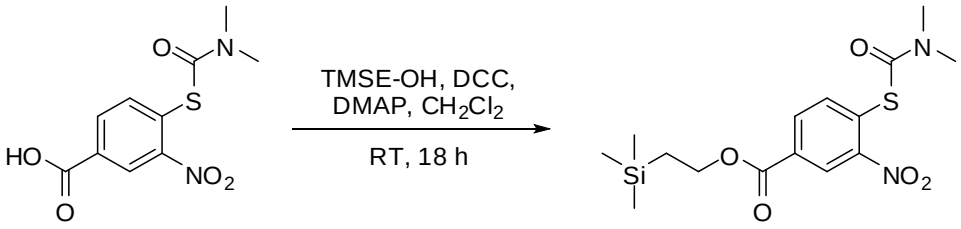
^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 8.51 (d, *J*=3.2 Hz, 1 H) 8.17 (d, *J*=7.9 Hz, 1 H) 7.58 (dd, *J*=6.7, 4.6 Hz, 1 H) 3.07 (d, *J*=22.4 Hz, 6 H)

^{13}C NMR: (75 MHz, CHLOROFORM-*d*) δ 162.99 (C) 148.28 (CH) 147.90 (CH) 126.95 (CH) 120.47 (C) 37.33 (CH_3) 37.01 (CH_3) ppm (quaternary carbon on position 2 not visible)

IR (HATR): 3071 (vw) 2936 (w) 1733 (w) 1673 (m) 1577 (w) 1541 (m) 1480 (w) 1441 (w) 1365 (m) 1256 (m) 1098 (m) 1064 (m) 1048 (m) 903 (w) 860 (w) 809 (w) 778 (w) 749 (w) 704 (w) 684 (m) 650 (w)

TLC: R_f = 0,14 (hexane/EtOAc 60/40)

2.3 TMSE-PROTECTION OF 4-S-(DIMETHYLTHIOCARBAMOYL)-3-NITROBENZOIC ACID

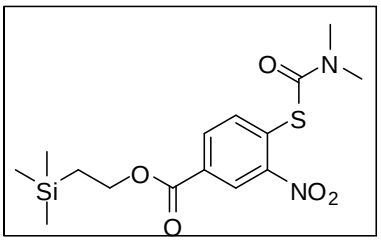


II.19-g **II.21**

2.3.1 PROCEDURE

To a solution of thiocarbamate **II.19-g** (4.00 g, 14.8 mmol, 1 eq) in 77 ml of CH_2Cl_2 is added subsequently DCC (3.06 g, 14.8 mmol, 1 eq), trimethylsilylethanol (2.12 ml, 14.8 mmol, 1 eq) and DMAP (0.362 g, 2.96 mmol, 0.2 eq). After 18 h of stirring at room temperature, the solvent is removed under pressure and the crude product is purified by column chromatography (eluent hexane/ethyl acetate 90/10), to deliver the desired product **II.21** as a yellow oil.

2.3.2 2-(TRIMETHYLSILYL)ETHYL-4-S-(DIMETHYLTHIOCARBAMOYL)-3-NITROBENZOATE **II.21**



Yield: 62% (yellow oil)

Formula: $C_{15}H_{22}N_2O_5SSi$

Molecular weight: 370,50 g/mol

t_{ret} = 20,0 min (Method A)

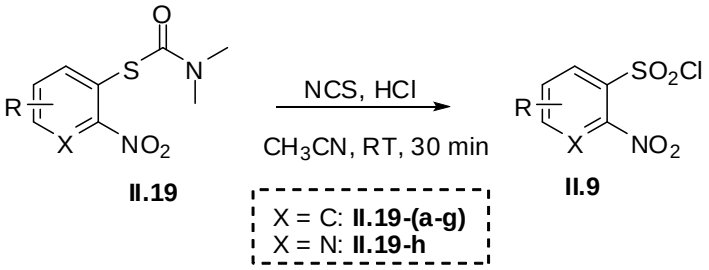
ES-MS [m/z (fragment, intensity)]: 371,0 ($M+H^+$, 100)

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 8.56 (d, *J*=1.5 Hz, 1 H) 8.19 (dd, *J*=8.3, 1.7 Hz, 1 H) 7.81 (d, *J*=8.3 Hz, 1 H) 4.46 (t, *J*=8.3 Hz, 5 H) 3.09 (d, *J*=28.8 Hz, 6 H) 1.15 (t, *J*=8.1 Hz, 2 H) 0.09 (s, 9 H)

^{13}C NMR: (75 MHz, CHLOROFORM-*d*) δ 164.23 (C) 163.43 (C) 151.72 (C) 137.72 (CH) 132.37 (CH) 132.03 (C) 129.83 (C) 125.61 (CH) 64.38 (CH2) 37.21 (CH_3) 17.43 (CH_2) -1,48 (CH_3) ppm (quaternary carbon on position 2 not visible)

TLC: R_f = 0,08 (hexane/EtOAc 85/15)

2.4 SYNTHESIS OF THE 2-NITROBENZENESULFONYLCHLORIDES



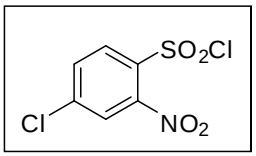
II.19 **II.9**

X = C: **II.19-(a-g)**
X = N: **II.19-h**

2.4.1 GENERAL PROCEDURE

The S-thiocarbamate **II.19** or **II.21** (1.00 mmol, 1.00 eq) is brought in a flask together with 2 ml of a 2 M HCl-acetonitril (1/5) mixture. NCS (4.00 mmol, 4.00 eq) is added to this suspension while it is stirred and maintained at room temperature using a water bath. After aproximately 30 min, a strong evolution of gas is observed and the suspension is turned into a bright yellow solution. Now, the reaction mixture is poured into a separating funnel together with 6 ml of isopropylether and washed 3 times with 5 ml of brine. The organic layer is then dryed over $MgSO_4$, evaporated under reduced pressure and purified using flash chromatography, yielding the desired sulfonyl chlorides **II.9**.

2.4.2 4-CHLORO-2-NITROBENZENESULFONYL CHLORIDE **II.9-A**



Eluent: hexane/ethyl acetate 95/5

Yield: 84% (slightly brown crystals)

Formula: $C_6H_3Cl_2NO_4S$

Molecular weight: 256,92 g/mol

LC-MS:
t_{ret} = 17,0 min (Method A), peak of the corresponding sulfonic acid also visible due to hydrolysis
ES-MS [m/z (fragment, intensity)]: 279,1 ($M+Na^+$, 100)

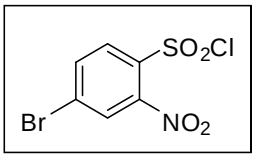
^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 8.20 (d, *J*=8.7 Hz, 1 H) 7.87 (d, *J*=2.1 Hz, 1 H) 7.81 (dd, *J*=8.5, 2.1 Hz, 1 H)

^{13}C NMR: (75 MHz, CHLOROFORM-*d*) δ 143.23 (C) 134.28 (C) 132.83 (CH) 131.57 (CH) 125.58 (CH) ppm (quaternary carbon on position 2 not visible)

IR (HATR): 3097 (w) 1584 (m) 1546 (s) 1462 (w) 1380 (s) 1355 (s) 1288 (w) 1259 (w) 1176 (s) 1158 (s) 1131 (m) 1105 (m) 1068 (w) 1044 (w) 1024 (w) 886 (m) 833 (m) 772 (s) 747 (m) 661 (w) 623 (m)

TLC: R_f = 0,37 (hexane/EtOAc 80/20)

2.4.3 4-BROMO-2-NITROBENZENESULFONYL CHLORIDE **II.9-B**



Eluent: hexane/ethyl acetate 95/5

Yield: 80% (yellow solid)

Formula: $C_6H_3BrClNO_4S$

Molecular weight: 300,51 g/mol

LC-MS:
t_{ret} = 17,3 min (Method A), peak of the corresponding sulfonic acid also visible due to hydrolysis
ES-MS [m/z (fragment, intensity)]: no ionisation

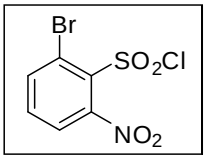
^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 8.10 (d, *J*=8.5 Hz, 1 H) 8.02 (d, *J*=1.7 Hz, 1 H) 7.98 (dd, *J*=8.5, 1.9 Hz, 1 H)

^{13}C NMR: (75 MHz, CHLOROFORM-*d*) δ 135.94 (CH) 134.67 (C) 131.43 (CH) 131.38 (C) 128.38 (CH) ppm (quaternary carbon on position 2 not visible)

IR (HATR): 3094 (w) 3008 (vw) 2896 (vw) 1578 (m) 1545 (s) 1461 (w) 1379 (m) 1352 (m) 1286 (w) 1261 (vw) 1173 (m) 1157 (m) 1129 (w) 1092 (m) 1045 (w) 874 (m) 832 (w) 758 (m) 746 (m) 704 (vw) 659 (w)

TLC: R_f = 0,35 (hexane/EtOAc 80/20)

2.4.4 6-BROMO-2-NITROBENZENESULFONYL CHLORIDE **II.9-C**



Eluent: hexane/ethyl acetate 80/20

Yield: 85% (pale brown powder)

Formula: $C_6H_3BrClNO_4S$

Molecular weight: 300,51 g/mol

LC-MS:
t_{ret} = 17,3 min (Method A), peak of the corresponding sulfonic acid also visible due to hydrolysis
ES-MS [m/z (fragment, intensity)]: no ionisation

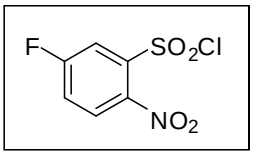
^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 8.05 (dd, *J*=8.1, 1.3 Hz, 1 H) 7.67 (t, *J*=7.9 Hz, 1 H) 7.58 (dd, *J*=7.9, 1.3 Hz, 1 H)

^{13}C NMR: (75 MHz, CHLOROFORM-*d*) δ ppm 138.97 (CH) 136.09 (CH) 123.86 (C) 123.25 (CH) ppm (quaternary carbons on position 1 and 2 not visible)

IR (HATR): 3073 (vw) 1551 (m) 1434 (w) 1390 (m) 1364 (m) 1265 (m) 1190 (m) 1136 (w) 1093 (w) 1040 (w) 895 (vw) 868 (vw) 801 m) 729 (s) 704 (m)

TLC: R_f = 0,72 (CH_2Cl_2)

2.4.5 5-FLUORO-2-NITROBENZENESULFONYL CHLORIDE **II.9-D**



Eluent: hexane/ethylacetate 90/10

Yield: 71% (slightly brown crystals)

Formula: $C_6H_3ClFNO_4S$

Molecular weight: 239,61 g/mol

LC-MS:
t_{ret} = 16,4 min (Method A), peak of the corresponding sulfonic acid also visible due to hydrolysis
ES-MS [m/z (fragment, intensity)]: no ionisation

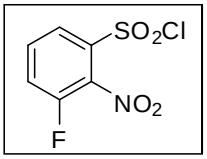
^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 7.92 - 8.07 (m, 2 H) 7.54 - 7.66 (m, 1 H)

^{13}C NMR: (75 MHz, CHLOROFORM-*d*) δ 163.19 (d, *J*=262.91, C) 143.42 (C) 138.24 (d, *J*=7.68, C) 128.14 (d, J=9.33, CH) 123.06 (d, *J*=22.5, CH) 118.40 (d, *J*=27.99, CH) ppm (quaternary carbon on position 2 not visible)

IR (HATR): 3107 (w) 2897 (vw) 1590 (m) 1541 (s) 1473 (m) 1378 (m) 1355 (m) 1311 (w) 1265 (m) 1224 (m) 1174 (s) 1125 (m) 1046 (w) 964 (vw) 910 (w) 886 (m) 846 (m) 834 (m) 746 (w) 685 (m)

TLC: R_f = 0,34 (hexane/EtOAc 80/20)

2.4.6 3-FLUORO-2-NITROBENZENESULFONYL CHLORIDE **II.9-E**



Eluent: hexane/ethyl acetate 80/20

Yield: 94% (yellow solid)

Formula: $C_6H_3ClFNO_4S$

Molecular weight: 239,61 g/mol

LC-MS:
t_{ret} = 6,1 min (method C), peak of the corresponding sulfonic acid also visible due to hydrolysis
ES-MS [m/z (fragment, intensity)]: 220,0 ($M-H^+$-Cl+OH, 100)

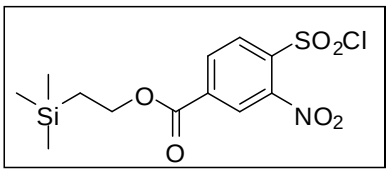
^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 8.01 (dt, *J*=7.9, 1.3 Hz, 1 H) 7.76 - 7.86 (m, 1 H) 7.72 (t, *J*=8.5 Hz, 1 H)

^{13}C NMR: (75 MHz, CHLOROFORM-*d*) δ 153.75 (d, *J*=264.01, C) 136.07 (C) 132.58 (d, *J*=7.68, CH) 125.02 (d, *J*=3.29, CH) 124.75 (d, *J*=19.21, CH) ppm (quaternary carbon on position 2 not visible)

IR (HATR): 3092 (w) 2903 (vw) 1735 (w) 1589 (w) 1552 (s) 1466 (m) 1446 (w) 1388 (m) 1358 (m) 1300 (w) 1268 (m) 1204 (m) 1174 (m) 1153 (w) 1126 (w) 1061 (w) 912 (m) 848 (m) 796 (m) 737 (m) 720 (m) 676 (w)

TLC: R_f = 0,26 (hexane/EtOAc 75/25)

2.4.7 (TRIMETHYLSILYL)ETHYL-4-CHLOROSULFONYL-3-NITROBENZOATE **II.9-F**



Eluent: hexane/ethyl acetate 95/5

Yield: 61% (brownish powder)

Formula: $C_{12}H_{16}ClNO_6SSi$

Molecular weight: 365,86 g/mol

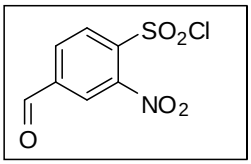
LC-MS:
t_{ret} = 7,4 min (Method C), peak of the corresponding sulfonic acid also visible due to hydrolysis
ES-MS [m/z (fragment, intensity)]: 346,0 ($M-Cl^-+OH^-$, 100)

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 8.40 - 8.50 (m, 2 H) 8.33 (d, *J*=8.1 Hz, 1 H) 4.45 - 4.57 (m, 2 H) 1.12 - 1.23 (m, 2 H) 0.10 (s, 9 H)

^{13}C NMR: (75 MHz, CHLOROFORM-*d*) δ 162.60 (C=O) 138.49 (C) 138.25 (C) 133.29 (CH) 130.72 (CH) 126.05 (CH) 65.60 (CH_2) 17.52 (CH_2) -1.50 (CH_3) ppm (quaternary carbon on position 2 not visible)

TLC: R_f = 0,14 (hexane/EtOAc 95/5)

2.4.8 4-FORMYL-2-NITROBENZENESULFONYL CHLORIDE **II.9-G**



Eluent: hexane/ethyl acetate 70/30

Yield: 95% (yellow solid)

Formula: $C_7H_4ClNO_5S$

Molecular weight: 249,63 g/mol

LC-MS:
t_{ret} = 5,4 min (method C), peak of the corresponding sulfonic acid also visible due to hydrolysis
ES-MS [m/z (fragment, intensity)]: 230,0 ($M-H^+-Cl+OH$, 100)

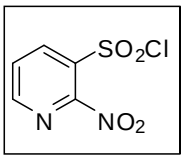
^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 10.18 (s, 1 H) 8.45 (d, *J*=8.5 Hz, 1 H) 8.26 - 8.39 (m, 2 H)

^{13}C NMR: (75 MHz, CHLOROFORM-*d*) δ ppm 187.67 (CH), 141.37 (C), 139.21 (C), 133.12 (CH), 131.58 (CH), 125.13 (CH) (quaternary carbon on position 2 not visible)

IR (HATR): 3403 (vw) 3099 (w) 2858 (w) 1708 (s) 1602 (w) 1546 (s) 1469 (w) 1415 (w) 1380 (s) 1353 (s) 1301 (w) 1268 (w) 1173 (s) 1118 (m) 1042 (w) 1006 (w) 944 (w) 904 (w) 838 (w) 817 (m) 748 (w) 722 (m) 687 (m) 655 (m)

TLC: R_f = 0,27 (hexane/EtOAc 60/40)

2.4.9 2-NITROPYRIDINE-3-SULFONYL CHLORIDE **II.9-H**



Eluent: hexane/ethyl acetate 90/10

Yield: 80% (pale yellow solid)

Formula: $C_5H_3ClN_2O_4S$

Molecular weight: 222,61 g/mol

LC-MS:
t_{ret} = 15,4 min (Method A), peak of the corresponding sulfonic acid also visible due to hydrolysis
ES-MS [m/z (fragment, intensity)]: no ionisation

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 8.87 (dd, *J*=4.7, 1.3 Hz, 1 H) 8.65 (dd, *J*=8.0, 1.4 Hz, 1 H) 7.85 - 7.98 (m, 1 H)

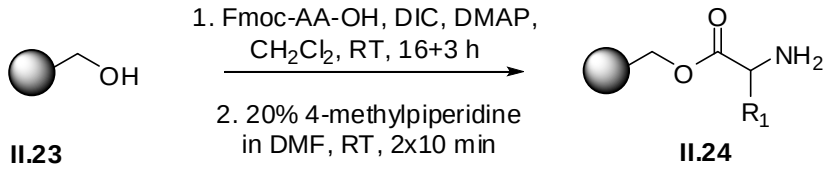
^{13}C NMR: (75 MHz, CHLOROFORM-*d*) δ 154.31 (CH) 139.96 (CH) 131.70 (C) 128.12 (CH) ppm (quaternary carbon on position 2 not visible)

IR (HATR): 3600-3100 (broad peak, w) 3081 (w) 1664 (w) 1555 (s) 1441 (w) 1413 (w) 1386 (m) 1368 (m) 1230 (w) 1176 (s) 1141 (m) 1064 (w) 1043 (w) 1028 (w) 858 (w) 810 (w) 773 (w) 752 (m) 730 (w) 656 (w) 644 (m)

TLC: R_f = 0,14 (hexane/EtOAc 70/30)

3 2,3-DIHYDRO-1,2,5-BENZOTHIADIAZEPIN-4(5*H*)-ONE-1,1-DIOXIDES VIA THE CYCLIZATION/RELEASE STRATEGY

3.1 α-AMINO ACID COUPLING ON WANG RESIN



II.23 **II.24**

3.1.1 GENERAL PROCEDURE

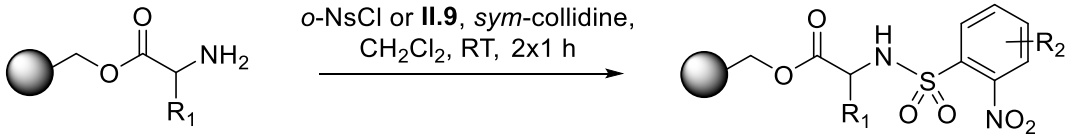
Preswell: Wang resin (1.50 g, 1.49 mmol, 1 eq) is preswollen first by suspending it in 20 ml of CH_2Cl_2 and by shaking it for 20 min. After filtration, this procedure is repeated for a second time.

Preactivation: To a stirring solution of an N^{α}-Fmoc-protected amino acid (2.97 mmol, 2 eq) in 20 ml CH_2Cl_2 at 0°C is added DIC (2.97 mmol, 2 eq). This reaction mixture is stirred for 20 min at 0°C.

Coupling: The preactivated reaction mixture is added to the preswollen Wang resin together with DMAP (0.30 mmol, 0.2 eq) and shaken for 16 h at room temperature. The resin was subsequently washed 3 times with DMF, MeOH and CH_2Cl_2 and this coupling procedure was repeated for a second time, shaking the resin 3 h before washing again with DMF, MeOH and CH_2Cl_2. The loading of the coupled resin was determined by Fmoc UV-quantification.

Deprotection: The resin is suspended in a solution of 20 ml 20% 4-methylpiperidine in DMF and shaken for 10 min. The resin is subsequently washed with DMF, MeOH and CH_2Cl_2 and this procedure is repeated for a second time, delivering the resin bound deprotected α-amino acid **II.24**.

3.2 NOSYL COUPLING

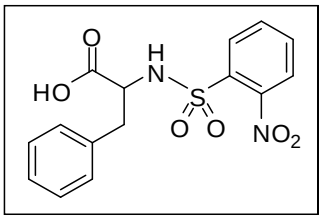


II.24 **II.25**

3.2.1 GENERAL PROCEDURE

The solid supported α-amino acid **II.24** (0.500 g, 0.37 mmol, 1 eq) is suspended in 10 ml of CH_2Cl_2 and shaken in the presence of *o*-NsCl or **II.9-(a-g)** (0.92 mmol, 2.5 eq) and *sym*-collidine (1,86 mmol, 5 eq). After 1 h shaking at room temperature, the resin is filtered off and washed subsequently with DMF, MeOH and CH_2Cl_2. This reaction is repeated for a second time, delivering the nosyl protected resin bound amino acid **II.25**.

This reaction was optimized for compound **II.25**, with R_1 = Bn and R_2 = H. LC-MS analysis after cleavage delivered the following result:



Formula: $C_{15}H_{14}N_2O_6S$

Molecular weight: 350,35 g/mol

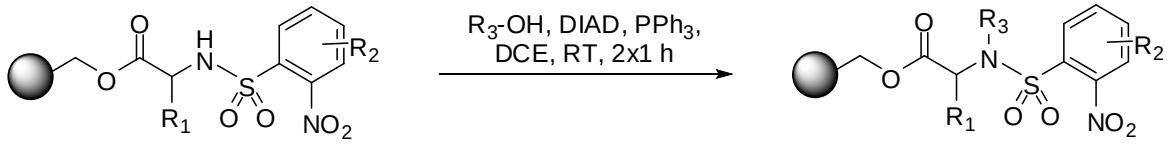
LC-MS:

t_{ret} = 11,5 min (Method A)

ES-MS [m/z (fragment, intensity)]: 349,0 ($M\text{-}H^+$, 100), 699,1 ($2M\text{-}H^+$, 20)

purity: 96%

3.3 MITSUNOBU-FUKUYAMA ALKYLATION

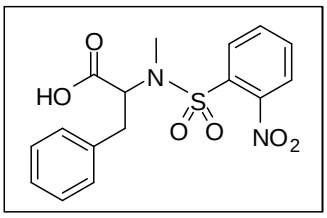


II.25 **II.36**

3.3.1 GENERAL PROCEDURE

Resin bound compound **II.25** (0.37 mmol, 1 eq) is suspended in 10 ml of 1,2-dichloroethane, followed by addition of respectively an alcohol (3.7 mmol, 10 eq), triphenylphosphine (0.488 g, 1.86 mmol, 5 eq) and DIAD (0.37 ml, 1.86 mmol, 5 eq). After shaking this yellow mixture for 1 h, the resin is filtered off and washed consecutively 3 times with DMF, MeOH and CH_2Cl_2. This procedure is repeated for a second time, yielding the desired alkylated compound **II.36**.

This reaction was optimized for compound **II.36**, with R_1 = Bn, R_2 = H and R_3 = Me. LC-MS analysis after cleavage delivered the following result:



Formula: $C_{16}H_{16}N_2O_6S$

Molecular weight: 364,37 g/mol

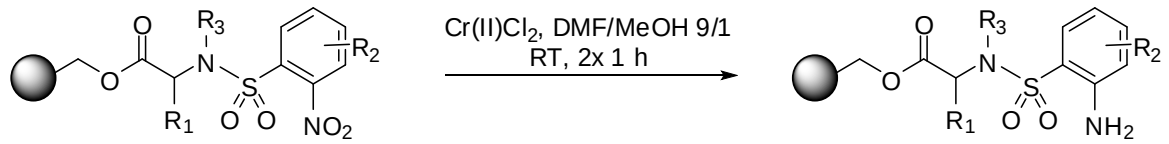
LC-MS:

t_{ret} = 11,9 min (Method A)

ES-MS [m/z (fragment, intensity)]: 363,0 ($M\text{-}H^+$, 100), 727,1 ($2M\text{-}H^+$, 40)

Purity: 88%

3.4 NITRO REDUCTION

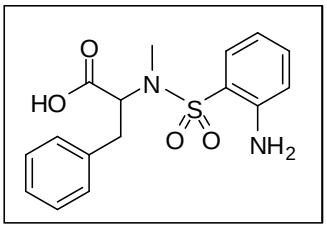


II.36 **II.37**

3.4.1 GENERAL PROCEDURE

To the resin bound compound **II.36** (0.37 mmol, 1 eq) is added 6 ml of a mixture of DMF/MeOH 9/1 and chromium(II) chloride (2.96 mmol, 8 eq). This green suspension is shaken for 1 h, followed by filtration and washing 3 times with DMF, MeOH and CH_2Cl_2. The reduction and washing procedure is repeated for a second time, delivering the desired aniline **II.37**.

This reaction was optimized for compound **II.37**, with R_1 = Bn, R_2 = H and R_3 = Me. LC-MS analysis after cleavage delivered the following result:



Formula: $C_{16}H_{18}N_2O_4S$

Molecular weight: 334,39 g/mol

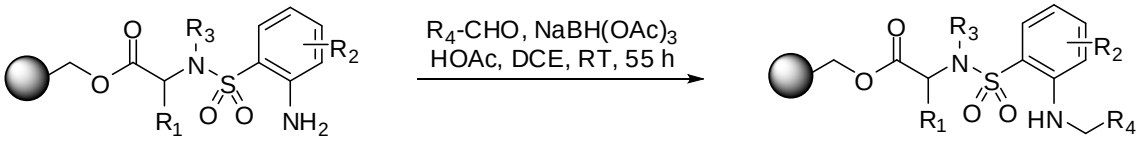
LC-MS:

t_{ret} = 11,4 min (t_{ret} = 12,2 min, 439,1 ($M-H^+$+106) = product + Wang linker) (Method A)

ES-MS [m/z (fragment, intensity)]: 333,0 ($M-H^+$, 100)

Purity: 81%

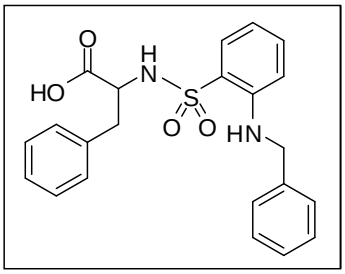
3.5 REDUCTIVE AMINATION OF ANILINE **II.37**



II.37 **II.38**

3.5.1 GENERAL PROCEDURE

The resin (0.16 mmol, 1 eq) is suspended in 10 ml 1,2-dichloroethane, followed by the consecutive addition of an aldehyde (1.60 mmol, 10 eq), acetic acid (0.093ml, 1.63 mmol, 10 eq) and sodium triacetoxyborohydride (0.206 g, 0.97 mmol, 6 eq). This mixture is stirred for 55 h, filtered off and washed consecutively 3 times with DMF, MeOH and CH_2Cl_2. This readily delivers the alkylated aniline **II.15**. This reaction was optimized for compound **II.54**, with R_1 = Bn, R_2 = H and R_3 = H. LC-MS analysis after cleavage from the solid support delivered the following result:



Formula: $C_{22}H_{22}N_2O_4S$

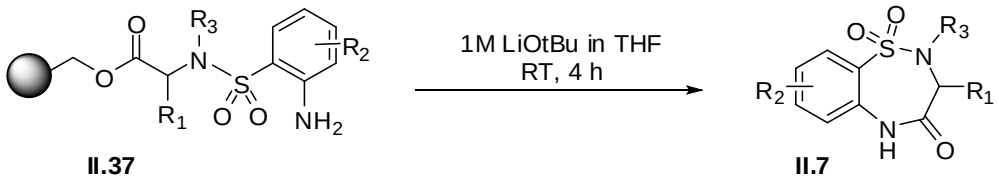
Molecular weight: 410,49 g/mol

LC-MS:

t_{ret} = 13,5 min (t_{ret} = 14,1 min, 515,1 ($M-H^+$+106) = product + Wang linker) (Method A)

ES-MS [m/z (fragment, intensity)]: 409,1 ($M-H^+$, 100), 819,2 ($2M-H^+$, 20)

3.6 RING CLOSURE USING BASIC CONDITIONS

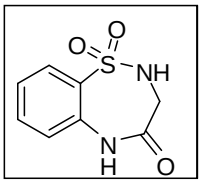


II.37 **II.7**

3.6.1 GENERAL PROCEDURE

To resin **II.37** (0.34 mmol, 1 eq) is added 4 ml of a 1 M solution of LiOtBu in THF. This suspension is shaken for 4 h at room temperature, followed by filtrating off the resin and washing it with THF. The filtrate is then evaporated under reduced pressure, redissolved in 12 ml of EtOAc and washed 2 times with a 5% solution of $NaHCO_3$ in water and 1 time with 10 ml brine. The organic phase is then dried over $MgSO_4$ and evaporated again to yield a brownish oil. This oil is purified using column chromatography or recrystallization, yielding the desired 2,3-dihydro-1,2,5-benzothiadiazepin-4(5*H*)-one-1,1-dioxides **II.7**.

3.6.2 2,3-DIHYDRO-1,2,5-BENZOTHIADIAZEPIN-4(5*H*)-ONE-1,1-DIOXIDE **II.7-A**



Formula: $C_8H_8N_2O_3S$ (white solid)

Molecular weight: 212,23 g/mol

Yield: 39%

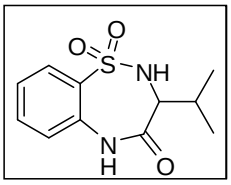
LC-MS:
t_{ret} = 12,0 min (Method A)
ES-MS [m/z (fragment, intensity)]: 211,0 ($M\text{-}H^+$, 100)

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 10.47 (s, 1 H) 8.46 (br. s., 1 H) 7.76 (dd, *J*=7.9, 1.5 Hz, 1 H) 7.51 - 7.61 (m, 1 H) 7.33 (dd, *J*=8.2, 1.0 Hz, 1 H) 7.20 (ddd, *J*=8.1, 7.2, 1.1 Hz, 1 H) 4.04 (s, 2 H)

^{13}C NMR: (75 MHz, DMSO-d_6) δ 171.43 (C=O) 134.59 (C) 133.43 (CH) 132.30 (C) 126.73 (CH) 122.76 (CH) 121.32 (CH) 46.60 (CH_2) ppm

TLC: R_f = 0,11 (CH_2Cl_2/EtOAc 80/20)

3.6.3 2,3-DIHYDRO-3-ISOPROPYL-1,2,5-BENZOTHIADIAZEPIN-4(5*H*)-ONE-1,1-DIOXIDE **II.7-B**



Formula: $C_{11}H_{14}N_2O_3S$ (white solid)

Molecular weight: 254,31 g/mol

Yield: 16%

LC-MS:

t_{ret} = 13,4 min (Method A)

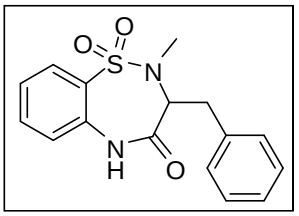
ES-MS [m/z (fragment, intensity)]: 253,0 ($M\text{-}H^+$, 100)

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 10.26 (s, 1 H) 8.40 (br. s., 1 H) 7.75 (dd, *J*=7.9, 1.3 Hz, 1 H) 7.53 (td, *J*=7.8, 1.6 Hz, 1 H) 7.14 - 7.34 (m, 2 H) 3.88 (d, *J*=4.3 Hz, 1 H) 2.25 (m, 1 H) 0.94 (dd, *J*=13.2, 6.8 Hz, 6 H)

^{13}C NMR: (75 MHz, DMSO-d_6) δ 172.10 (C=O) 134.07 (C) 133.08 (CH) 131.83 (C) 127.17 (CH) 123.14 (CH) 121.75 (CH) 59.55 (CH) 28.67 (CH) 19.34 (CH_3) 17.17 (CH_3) ppm

TLC: R_f = 0,28 (pentaan/EtOAc 60/40)

3.6.4 3-BENZYL-2,3-DIHYDRO-2-METHYL-1,2,5-BENZOTHIADIAZEPIN-4(5*H*)-ONE-1,1-DIOXIDE **II.7-C**



Formula: $C_{16}H_{16}N_2O_3S$ (white solid)

Molecular weight: 316,37 g/mol

Yield: 38%

LC-MS:

t_{ret} = 15,7 min (Method A)

ES-MS [m/z (fragment, intensity)]: 315,0 ($M\text{-}H^+$, 100)

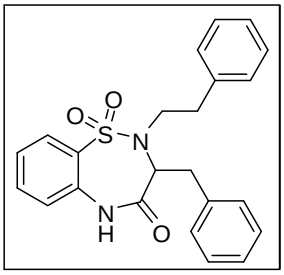
HR-MS (ESI): calculated for [$M\text{-}H^+$] = 316,0809, found 315,0815

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 10.56 (s, 1 H) 7.72 (dd, *J*=7.9, 1.5 Hz, 1 H) 7.58 (ddd, *J*=8.4, 7.2, 1.6 Hz, 1 H) 7.15 - 7.41 (m, 7 H) 4.76 (dd, *J*=10.4, 5.1 Hz, 1 H) 3.35 - 3.47 (m, 1 H) 3.01 (dd, *J*=14.4, 10.1 Hz, 1 H) 2.61 (s, 3 H)

^{13}C NMR: (75 MHz, DMSO-d_6) δ 170.93 (C=O) 137.37 (C) 133.85 (C) 133.72 (CH) 129.37 (CH) 128.80 (C) 128.10 (CH) 126.31 (CH) 123.40 (CH) 121.77 (CH) 61,55 (CH) 34.86 (CH_2) 32.40 (CH_3) ppm

TLC: R_f = 0,09 (pentaan/EtOAc 80/20)

3.6.5 3-BENZYL-2,3-DIHYDRO-2-(2-PHENYL)ETHYL-1,2,5-BENZOTHIADIAZEPIN-4(5*H*)-ONE-1,1-DIOXIDE **II.7-D**



Formula: $C_{23}H_{22}N_2O_3S$ (white solid)

Molecular weight: 406,50 g/mol

Yield: 54%

LC-MS:

t_{ret} = 18,3 min (Method A)

ES-MS [m/z (fragment, intensity)]: 405,1 ($M\text{-}H^+$, 100)

HR-MS (ESI): calculated for [$M\text{-}H^+$] = 405,1278, found 405,1288

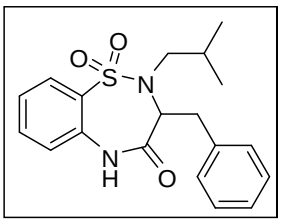
^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 10.54 (s, 1 H) 7.74 (d, *J*=7.9 Hz, 1 H) 7.56 (t, *J*=7.7 Hz, 1 H) 7.07 - 7.39 (m, 10 H) 6.95 (d, *J*=7.2 Hz, 2 H) 4.77 (dd, *J*=9.8, 4.7 Hz, 1 H) 3.50 (dd, *J*=13.9, 4.7 Hz, 1 H) 2.95 - 3.16 (m, 2 H) 2.76 (ddd, *J*=14.0, 11.6, 5.5 Hz, 1 H) 2.33 (td, *J*=12.0, 5.4 Hz, 1 H) 2.11 (td, *J*=12.2, 4.9 Hz, 1 H)

^{13}C NMR: (75 MHz, DMSO-d_6) δ 171.77 (C=O) 137.83 (C) 137.75 (C) 135.09 (C) 133.83 (CH) 129.82 (CH) 129.23 (C) 128.43 (CH) 128.36 (CH) 128.18 (CH) 127.50 (CH) 126.41 (CH) 126.34 (CH) 123.00 (CH) 121.40 (CH) 64,61 (CH) 50.80 (CH_2) 37.97 (CH_2) 34.26 (CH_2) ppm

IR (HATR): 3214 (vw) 3064 (w) 3026 (w) 2931 (w) 1670 (w) 1596 (w) 1584 (w) 1479 (w) 1454 (w) 1430 (w) 1371 (w) 1340 (w) 1302 (w) 1220 (vw) 1164 (w) 1138 (w) 1094 (vw) 758 (w) 699 (w)

TLC: R_f = 0,15 (pentaan/EtOAc 80/20)

3.6.6 3-BENZYL-2,3-DIHYDRO-2-ISOBUTYL-1,2,5-BENZOTHIADIAZEPIN-4(5*H*)-ONE-1,1-DIOXIDE **II.7-E**



Formula: $C_{19}H_{22}N_2O_3S$ (white solid)

Molecular weight: 358,46 g/mol

Yield: 41%

LC-MS:

t_{ret} = 18,4 min (Method A)

ES-MS [m/z (fragment, intensity)]: 357,1 ($M\text{-}H^+$, 100)

HR-MS (ESI): calculated for [$M\text{-}H^+$] = 357,1278, found 357,1289

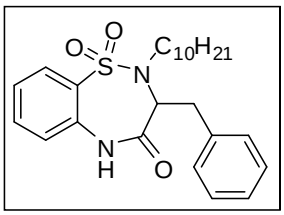
^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 10.55 (s, 1 H) 7.72 (dd, *J*=7.8, 1.2 Hz, 1 H) 7.52 - 7.63 (m, 1 H) 7.15 - 7.38 (m, 7 H) 4.61 (dd, *J*=9.6, 5.1 Hz, 1 H) 3.50 (dd, *J*=14.1, 5.1 Hz, 1 H) 3.18 (dd, *J*=14.0, 9.7 Hz, 1 H) 2.68 (dd, *J*=13.9, 5.1 Hz, 1 H) 2.35 (dd, *J*=13.8, 9.5 Hz, 1 H) 1.31 - 1.45 (m, 1 H) 0.55 (d, *J*=6.6 Hz, 3 H) 0.42 (d, *J*=6.4 Hz, 3 H)

^{13}C NMR: (75 MHz, DMSO-d_6) δ 171.97 (C=O) 137.75 (C) 134.98 (C) 133.82 (CH) 129.70 (CH) 128.97 (C) 128.15 (CH) 127.73 (CH) 126.33 (CH) 123.05 (CH) 121.29 (CH) 64.78 (CH) 56.55 (CH_2) 38.24 (CH_2) 26.64 (CH) 19.71 (CH_3) 19.25 (CH_3) ppm

IR (HATR): 2954 (w) 2358 (w) 2336 (w) 1659 (m) 1584 (w) 1478 (w) 1366 (m) 1345 (m) 1302 (w) 1166 (m) 1132 (w) 1077 (w) 1038 (w) 925 (vw) 861 (w) 799 (w) 762 (m) 740 (m) 717 (m) 696 (m) 659 (vw)

TLC: R_f = 0,12 (pentaan/EtOAc 80/20)

3.6.7 3-BENZYL-2-DECYL-2,3-DIHYDRO-1,2,5-BENZOTHIADIAZEPIN-4(5*H*)-ONE-1,1-DIOXIDE **II.7-F**



Formula: $C_{25}H_{34}N_2O_3S$ (white solid)

Molecular weight: 442,61 g/mol

Yield: 35%

LC-MS:

t_{ret} = 14,9 min (Method B)

ES-MS [m/z (fragment, intensity)]: 441,2 ($M-H^+$, 100)

HR-MS (ESI): calculated for [$M-H^+$] = 441,2217, found 441,2218

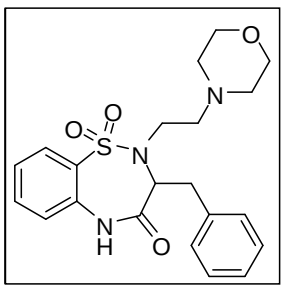
^{1}H NMR: (300 MHz, Acetone-d_6) δ ppm 9.45 (br. s., 1 H) 7.81 (d, *J*=7.9 Hz, 1 H) 7.58 (t, *J*=7.8 Hz, 1 H) 7.19 - 7.42 (m, 7 H) 4.56 (dd, *J*=9.8, 4.7 Hz, 1 H) 3.64 (dd, *J*=14.1, 4.7 Hz, 1 H) 3.27 (dd, *J*=14.0, 9.9 Hz, 1 H) 2.86 - 3.00 (m, 1 H) 2.64 - 2.80 (m, 1 H) 0.92 - 1.35 (m, 16 H) 0.87 (t, *J*=6.8 Hz, 3 H)

^{13}C NMR: (75 MHz, Acetone-d_6) δ 173.35 (C=O) 139.65 (C) 136.78 (C) 135.07 (CH) 131.73 (C) 131.41 (CH) 129.70 (CH) 129.41 (CH) 127.89 (CH) 124.50 (CH) 122.70 (CH) 66.44 (CH) 51.12 (CH_2) 40.05 (CH_2) 33.17 (CH_2) 30.95 (CH_2) 30.69 (CH_2) 30.44 (CH_2) 30.18 (CH_2) 29.65 (CH_2) 27.65 (CH_2) 23.90 (CH_2) 14.95 (CH_3) ppm

IR (HATR): 3077 (w) 1571 (w) 1538 (m) 1434 (w) 1387 (m) 1366 (w) 1184 (w) 1136 (w) 1090 (w) 1039 (w) 868 (vw) 804 (w) 748 (w) 728 (w) 717 (w) 706 (w)

TLC: R_f = 0,28 (hexane/EtOAc 60/40)

3.6.8 3-BENZYL-2,3-DIHYDRO-2-(N-MORPHOLINOETHYL)-1,2,5-BENZOTHIADIAZEPIN-4(5*H*)-ONE-1,1-DIOXIDE **II.7-G**



Formula: $C_{21}H_{25}N_3O_4S$ (white solid)

Molecular weight: 415,51 g/mol

Yield: 33%

LC-MS:
t_{ret} = 15,5 min (Method A)
ES-MS [m/z (fragment, intensity)]: 414,1 ($M-H^+$, 100)

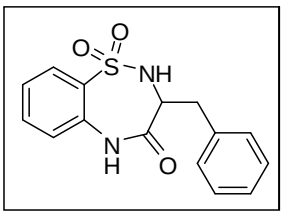
HR-MS (ESI): calculated for [$M-H^+$] = 414,1488, found 414,1487

^{1}H NMR: (300 MHz, CHLOROFORM-*d*) δ ppm 8.17 (br. s., 1 H) 7.81 (d, *J*=7.5 Hz, 1 H) 7.41 (br. s., 1 H) 7.21 - 7.36 (m, 5 H) 7.13 (t, *J*=7.9 Hz, 1 H) 6.92 (br. s., 1 H) 4.56 (d, *J*=5.5 Hz, 1 H) 3.62 (d, *J*=12.4 Hz, 1 H) 3.43 (br. s., 4 H) 3.21 - 3.37 (m, 1 H) 3.02 (br. s., 1 H) 2.75 (br. s., 1 H) 1.77 - 2.22 (m, 6 H)

^{13}C NMR: (75 MHz, CHLOROFORM-*d*) δ 172.37 (C=O) 137.52 (C) 134.14 (C) 133.61 (CH) 131.09 (C) 129.78 (CH) 128.66 (CH) 128.11 (CH) 126.87 (CH) 123.77 (CH) 120.65 (CH) 66.62 (CH_2) 65.47 (CH) 56.71 (CH_2) 53.43 (CH_2) 46.02 (CH_2) 38.66 (CH_2) ppm

TLC: R_f = 0,06 (CH_2Cl_2/EtOAc 95/5)

3.6.9 2,3-DIHYDRO-1,2,5-BENZOTHIADIAZEPIN-4(5*H*)-ONE-1,1-DIOXIDE **II.7-H**



Formula: $C_{15}H_{14}N_2O_3S$ (white solid)

Molecular weight: 302,35 g/mol

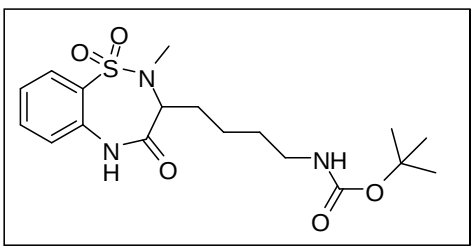
Yield: 26%

LC-MS:
t_{ret} = 14,4 min (Method A)
ES-MS [m/z (fragment, intensity)]: 301,0 ($M-H^+$, 100)
Purity: 96%

^{1}H NMR: (300 MHz, DMSO-d_6) δ ppm 10.55 (s, 1 H) 7.72 (dd, *J*=7.9, 1.5 Hz, 1 H) 7.58 (ddd, *J*=8.4, 7.1, 1.5 Hz, 1 H) 7.16 - 7.37 (m, 7 H) 4.74 (dd, *J*=10.1, 4.8 Hz, 1 H) 3.35 - 3.43 (m, 1 H) 3.01 (dd, *J*=14.4, 10.1 Hz, 1 H) 2.61 (s, 3 H)

^{13}C NMR: (75 MHz, DMSO-d_6) δ ppm 170.88 (C=O) 137.34 (C) 133.84 (C) 133.68 (CH) 129.34 (CH) 128.78 (C) 128.13 (CH) 128.07 (CH) 126.28 (CH) 123.37 (CH) 121.75 (CH) 61.56 (CH) 34.86 (CH_2) 32.39 (CH_3)

3.6.10 2,3-DIHYDRO-3-(4-*TERT*-BUTOXYCARBONYLAMINO)BUTYL-2-METHYL-1,2,5-BENZOTHIADIAZEPIN-4(5*H*)-ONE-1,1-DIOXIDE **II.7-I**



Formula: $C_{18}H_{27}N_3O_5S$ (white solid)

Molecular weight: 397,49 g/mol

Yield: 54%

LC-MS:
t_{ret} = 15,6 min (Method A)

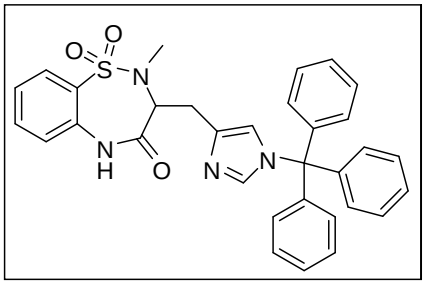
ES-MS [m/z (fragment, intensity)]: 396,1 ($M\text{-}H^+$, 100)
purity: 99%

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 8.73 (app d, *J*=33.5, 1 H) 7.94 (d, *J*=7.9 Hz, 1 H) 7.51 (t, *J*=7.8 Hz, 1 H) 7.18 - 7.25 (m, 1 H) 7.06 (dd, *J*=8.2, 2.9 Hz, 1 H) 4.61 (br. s., 1 H) 4.52 (dd, *J*=9.9, 4.8 Hz, 1 H) 3.16 (d, *J*=5.1 Hz, 2 H) 2.79 (s, 3 H) 2.05 - 2.22 (m, 1 H) 1.76 - 1.93 (m, 1 H) 1.49 - 1.73 (m, 4 H) 1.44 (s, 9 H)

^{13}C NMR: (75 MHz, CHLOROFORM-*d*) δ 172.36 (C=O) 133.67 (CH) 132.27 (C) 129.65 (C) 129.37 (CH) 124.31 (CH) 121.41 (CH) 58.95 (CH_2) 40.23 (C) 30.64 (CH_3) 29.37 (CH_2) 28.40 (CH_3) 27.49 (CH_2) 22.45 (CH_2) ppm

TLC: R_f = 0,10 (hexane/EtOAc 65/35)

3.6.11 2,3-DIHYDRO-2-METHYL-3-(1-TRITYLIMIDAZOL-4-YLMETHYL)-1,2,5-BENZOTHIADIAZEPIN-4(5H)-ONE-1,1-DIOXIDE **II.7-J**



Formula: $C_{32}H_{28}N_4O_3S$ (white solid)

Molecular weight: 548,65 g/mol

Yield: 38%

LC-MS:
t_{ret} = 18,2 min (Method A)
ES-MS [m/z (fragment, intensity)]: 547.1 ($M\text{-}H^+$, 100)

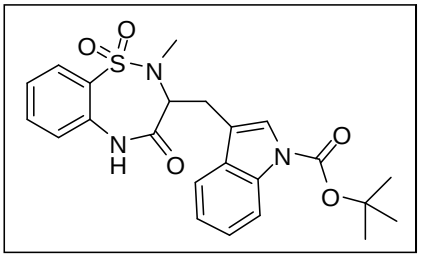
HR-MS (ESI): calculated for [$M\text{-}H^+$] = 547,1804, found 547,1797

^{1}H NMR: (300 MHz, DICHLOROMETHANE-d_2) δ ppm 8.61 (br. s., 1 H) 7.86 (d, *J*=7.7 Hz, 1 H) 7.46 (t, *J*=6.6 Hz, 1 H) 7.29 - 7.42 (m, 10 H) 7.12 - 7.26 (m, 7 H) 7.07 (d, *J*=6.6 Hz, 1 H) 6.75 (s, 1 H) 4.76 (d, *J*=6.2 Hz, 1 H) 3.44 (dd, *J*=15.3, 3.2 Hz, 1 H) 3.01 (dd, *J*=14.4, 10.3 Hz, 1 H) 2.69 (s, 3 H)

^{13}C NMR: (75 MHz, DICHLOROMETHANE-d_2) δ 172.40 (C=O) 143.17 (C) 138.75 (CH) 137.01 (C) 134.21 (CH) 133.87 (C) 130.40 (CH) 130.08 (C) 129.49 (CH) 128.61 (CH) 128.49 (CH) 124.47 (CH) 122.00 (CH) 120.75 (CH) 75.83 (C) 61.78 (CH) 33.11 (CH_3) 29.65 (CH_2) ppm

TLC: R_f = 0,04 (CH_2Cl_2/EtOAc 70/30)

3.6.12 3-(N-*TERT*-BUTOXYCARBONYLINDOL-3-YLMETHYL)-2,3-DIHYDRO-2-METHYL-1,2,5-BENZOTHIADIAZEPIN-4(5*H*)-ONE-1,1-DIOXIDE **II.7-K**



Formula: $C_{23}H_{25}N_3O_5S$ (white solid)

Molecular weight: 455,53 g/mol

Yield: 57%

LC-MS:
t_{ret} = 18,4 min (Method A)
ES-MS [m/z (fragment, intensity)]: 454,1 ($M-H^+$, 100)

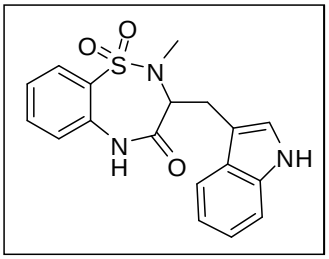
HR-MS (ESI): calculated for [$M-H^+$] = 454,1437, found 454,1436

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 8.41 (s, 1 H) 8.14 (d, *J*=8.3 Hz, 1 H) 7.94 (dd, *J*=7.9, 1.0 Hz, 1 H) 7.68 (s, 1 H) 7.61 (d, *J*=7.3 Hz, 1 H) 7.50 (t, *J*=7.7 Hz, 1 H) 7.29 - 7.37 (m, 1 H) 7.19 – 7.26 (m, 2H) 7.00 (d, *J*=8.1 Hz, 1 H) 4.77 - 4.89 (m, 1 H) 3.70 (dd, *J*=15.4, 5.7 Hz, 1 H) 3.24 (dd, *J*=15.4, 8.5 Hz, 1 H) 2.79 (s, 3 H) 1.67 (s, 9 H)

^{13}C NMR: (75 MHz, CHLOROFORM-*d*) δ 171.61 (C=O) 149.65 (C) 133.77 (CH) 132.52 (C) 130.20 (C) 129.68 (C) 129.29 (CH) 124.58 (CH) 124.49 (CH) 124.40 (CH) 122.60 (CH) 121.31 (CH) 118.62 (CH) 115.34 (CH) 115.20 (C) 83.63 (C) 60.19 (CH) 61.78 (CH) 32.42 (CH_3) 28.21 (CH_3) 25.64 (CH_2) ppm

TLC: R_f = 0,11 (hexane/EtOAc 85/25)

3.6.13 2,3-DIHYDRO-3-(2-INDOLYLMETHYL)-2-METHYL-1,2,5-BENZOTHIADIAZEPIN-4(5*H*)-ONE-1,1-DIOXIDE **II.7-L**



Formula: $C_{18}H_{17}N_3O_5S$ (white solid)

Molecular weight: 355,41 g/mol

Yield: 44%

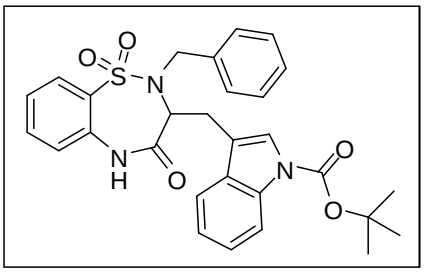
HR-MS (ESI): calculated for [$M-H^+$] = 354,0918, found 354,0931

^{1}H NMR: (300 MHz, CHLOROFORM-*d*) δ ppm 8.08 (br. s., 1 H) 7.94 (dd, *J*=8.1, 1.5 Hz, 2 H) 7.67 (d, *J*=7.9 Hz, 1 H) 7.45 - 7.55 (m, 1 H) 7.39 (d, *J*=7.9 Hz, 1 H) 7.33 (d, *J*=2.4 Hz, 1 H) 7.10 - 7.26 (m, 3 H) 6.95 (d, *J*=8.1 Hz, 1 H) 4.82 (dd, *J*=8.7, 5.8 Hz, 1 H) 3.77 (ddd, *J*=15.5, 5.7, 0.8 Hz, 1 H) 3.33 (dd, *J*=15.4, 8.7 Hz, 1 H) 2.77 (s, 3 H)

^{13}C NMR: (75 MHz, CHLOROFORM-*d*) δ 171.63 (C=O) 147.18 (C) 136.01 (C) 133.71 (CH) 132.62 (C) 129.69 (C) 129.29 (CH) 127.32 (C) 124.31 (CH) 123.32 (CH) 122.15 (CH) 121.21 (CH) 119.61 (CH) 118.39 (CH) 111.20 (CH) 110.46 (C) 60.54 (CH) 32.28 (CH_3) 25.51 (CH_2) ppm

TLC: R_f = 0,10 (CH_2Cl_2/EtOAc 60/40)

3.6.14 2-BENZYL-3-(N-*TERT*-BUTOXYCARBONYL-2-INDOLYLMETHYL)-2,3-DIHYDRO-1,2,5-BENZOTHIADIAZEPIN-4(5*H*)-ONE-1,1-DIOXIDE **II.7-M**



Formula: $C_{29}H_{29}N_3O_5S$ (white solid)

Molecular weight: 531,62 g/mol

Yield: 62%

LC-MS:
t_{ret} = 19,8 min (Method A)
ES-MS [m/z (fragment, intensity)]: 530,0 ($M-H^+$, 100)
purity: 97%

HR-MS (ESI): calculated for [$M-H^+$] = 530,1755, found 530,1771

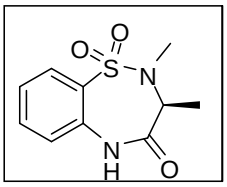
^{1}H NMR: (300 MHz, CHLOROFORM-*d*) δ ppm 8.88 (br. s., 1 H) 8.06 (d, *J*=8.1 Hz, 1 H) 7.94 (dd, *J*=7.9, 1.5 Hz, 1 H) 7.39 - 7.53 (m, 2 H) 7.32 - 7.38 (m, 1 H) 7.12 - 7.31 (m, 3 H) 6.91 - 7.11 (m, 4 H) 6.78 - 6.90 (m, 2 H) 4.58 (dd, *J*=8.5, 5.3 Hz, 1 H) 3.98 - 4.13 (m, 2 H) 3.54 - 3.68 (m, 1 H) 3.25 - 3.42 (m, 1 H) 1.68 (s, 9 H)

^{13}C NMR: (75 MHz, CHLOROFORM-*d*) δ 172.79 (C=O) 149.55 (C) 135.36 (C) 134.28 (C) 133.86 (CH) 130.29 (C) 130.10 (C) 128.56 (CH) 128.50 (CH) 128.12 (CH) 127.96 (CH) 124.75 (CH) 124.24 (CH) 123.98 (CH) 122.41 (CH) 121.07 (CH) 118.70 (CH) 115.74 (C) 115.23 (CH) 83.41 (C) 62.16 (CH_2) 52.82 (CH_2) 28.41 (CH_2) 28.24 (CH_3) ppm

IR (HATR): 3058 (vw) 2980 (w) 2932 (vw) 1727 (m) 1681 (m) 1596 (w) 1583 (w) 1478 (m) 1452 (m) 1429 (w) 1368 (m) 1336 (m) 1308 (w) 1255 (w) 1154 (s) 1086 (m) 1016 (w) 947 (vw) 917 (vw) 855 (w) 835 (vw) 760 (m) 732 (s) 703 (m) 646 (vw)

TLC: R_f = 0,05 (hexane/EtOAc 80/20)

3.6.15 (3S)-2,3-DIHYDRO-2,3-DIMETHYL-1,2,5-BENZOTHIADIAZEPIN-4(5*H*)-ONE-1,1-DIOXIDE **II.7-N**



Formula: $C_{10}H_{12}N_2O_3S$ (white solid)

Molecular weight: 240,28 g/mol

Yield: 58%

LC-MS:
t_{ret} = 13,0 min (Method A)
ES-MS [m/z (fragment, intensity)]: 239,0 ($M-H^+$, 100)

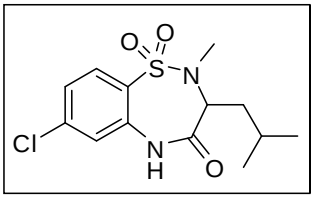
HR-MS (ESI): calculated for [$M-H^+$] = 239,0496, found 239,0505

^{1}H NMR ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 8.38 (br. s., 1 H) 7.95 (dd, *J*=7.9, 1.5 Hz, 1 H) 7.51 (ddd, *J*=8.1, 7.4, 1.6 Hz, 1 H) 7.20 - 7.30 (m, 1 H) 7.02 (d, *J*=8.3 Hz, 1 H) 4.68 (q, *J*=7.0 Hz, 1 H) 2.81 (s, 3 H) 1.60 (s, 3 H)

^{13}C NMR: (75 MHz, CHLOROFORM-*d*) δ 172,65 (C=O) 133.77 (CH) 132.65 (C) 129.37 (CH) 129.18 (C) 124.31 (CH) 121.30 (CH) 55.65 (CH) 31.00 (CH_3) 15.27 (CH_3) ppm

TLC: R_f = 0,21 (hexane/EtOAc 70/30)

3.6.16 7-CHLORO-2,3-DIHYDRO-3-ISOBUTYL-2-METHYL-1,2,5-BENZOTHIADIAZEPIN-4(5*H*)-ONE-1,1-DIOXIDE **II.7-O**



Formula: $C_{13}H_{17}ClN_2O_3S$ (white solid)

Molecular weight: 316,80 g/mol

Yield: 40%

LC-MS:

t_{ret} = 17,1 min (Method A)

ES-MS [m/z (fragment, intensity)]: 314,9 (M(^{35}Cl)-H$^+$, 100), 317,0 (M(^{37}Cl)-H$^+$, 30)

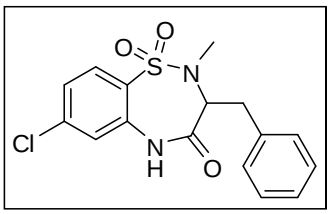
HR-MS (ESI): calculated for [M-H$^+$] = 315,0576, found 315,0586

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 8.24 (s, 1 H) 7.90 (d, *J*=8.5 Hz, 1 H) 7.22 (dd, *J*=8.5, 1.9 Hz, 1 H) 7.01 (d, *J*=1.7 Hz, 1 H) 4.67 (dd, *J*=10.0, 4.0 Hz, 1 H) 2.79 (s, 3 H) 1.74 - 1.99 (m, 3 H) 1.02 (t, *J*=6.7 Hz, 6 H)

^{13}C NMR: (300 MHz, CHLOROFORM-*d*) δ 172.65 (C=O) 139.58 (C) 133.39 (C) 130.93 (CH) 128.03 (C) 124.45 (CH) 120.77 (CH) 57.44 (CH) 36.78 (CH_2) 30.50 (CH_3) 23.91 (CH) 23.25 (CH_3) 21.09 (CH_3) ppm

TLC: R_f = 0,54 (hexane/EtOAc 60/40)

3.6.17 3-BENZYL-7-CHLORO-2,3-DIHYDRO-2-METHYL-1,2,5-BENZOTHIADIAZEPIN-4(5H)-ONE-1,1-DIOXIDE **II.7-P**



Formula: $C_{16}H_{15}ClN_2O_3S$ (white solid)

Molecular weight: 350,82 g/mol

Yield: 23%

LC-MS:

t_{ret} = 16,8 min (Method A)

ES-MS [m/z (fragment, intensity)]: 348,9 ((M(^{35}Cl)-H$^+$, 75), 351,0 (M(^{37}Cl)-H$^+$, 25)

purity: 97%

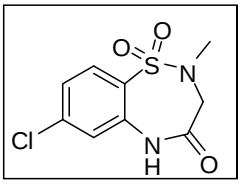
HR-MS (ESI): calculated for [M-H$^+$] = 349,0419, found 349,0427

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 10.64 (s, 1 H) 7.73 (d, *J*=8.7 Hz, 1 H) 7.40 (d, *J*=2.1 Hz, 1 H) 7.14 - 7.36 (m, 6 H) 4.80 (dd, *J*=10.2, 4.7 Hz, 1 H) 3.37 (dd, *J*=14.5, 4.7 Hz, 1 H) 3.01 (dd, *J*=14.4, 10.3 Hz, 1 H) 2.61 (s, 3 H)

^{13}C NMR: (75 MHz, DMSO-d_6) δ 171.00 (C=O) 137.75 (C) 137.18 (C) 135.40 (C) 130.10 (CH) 129.35 (CH) 128.10 (CH) 127.74 (C) 126.34 (CH) 123.13 (CH) 120.88 (CH) 61.67 (CH) 34.88 (CH_2) 32.45(CH_3) ppm

TLC: R_f = 0,15 (hexane/EtOAc 80/20)

3.6.18 7-CHLORO-2,3-DIHYDRO-2-METHYL-1,2,5-BENZOTHIADIAZEPIN-4(5*H*)-ONE-1,1-DIOXIDE **II.7-Q**



Formula: $C_9H_9ClN_2O_3S$ (white solid)

Molecular weight: 260,70 g/mol

Yield: 48%

LC-MS:
t_{ret} = 13,9 min (Method A)
ES-MS [m/z (fragment, intensity)]: 258,9 (M(^{35}Cl)-H$^+$, 75), 260,9 (M(^{37}Cl)-H$^+$, 25)

HR-MS (ESI): calculated for [M-H$^+$] = 258,9950, found 258,9959

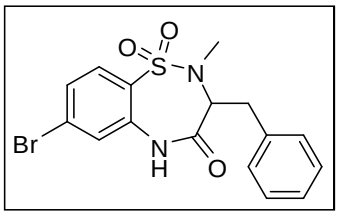
^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 10.73 (s, 1 H) 7.78 (d, *J*=8.5 Hz, 1 H) 7.46 (d, *J*=1.9 Hz, 1 H) 7.32 (dd, *J*=8.5, 1.9 Hz, 1 H) 4.27 (s, 2 H) 2.68 - 2.77 (m, 3 H)

^{13}C NMR: (75 MHz, DMSO-d_6) δ 170.47 (C=O) 138.29 (C) 136.16 (C) 130.22 (CH) 126.48 (C) 122.96 (CH) 120.76 (CH) 53.99 (CH_2) 36.02 (CH_3) ppm

IR (HATR): 3320 (w) 3064 (w) 3026 (w) 2924 (w) 1685 (m) 1660 (m) 1577 (m) 1495 (w) 1465 (w) 1455 (w) 1389 (m) 1358 (m) 1335 (m) 1296 (m) 1225 (w) 1166 (m) 1142 (m) 1104 (m) 1070 (w) 1045 (w) 982 (vw) 960 (w) 929 (w) 887 (w) 874 (w) 809 (m) 764 (m) 749 (m) 722 (m) 695 (m) 668 (w) 650 (w) 613 (w)

TLC: R_f = 0,10 (hexane/acetone 80/20)

3.6.19 3-BENZYL-7-BROMO-2,3-DIHYDRO-2-METHYL-1,2,5-BENZOTHIADIAZEPIN-4(5*H*)-ONE-1,1-DIOXIDE **II.7-R**



Formula: $C_{16}H_{15}BrN_2O_3S$ (white solid)

Molecular weight: 395,27 g/mol

Yield: 11%

LC-MS:

t_{ret} = 16,9 min (Method A)

ES-MS [m/z (fragment, intensity)]: 393,0 ((M(^{79}Br)-H$^+$, 50), 395,0 (M(^{81}Br)-H$^+$, 50)
Purity: 98%

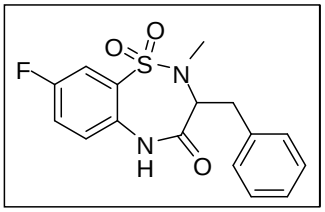
HR-MS (ESI): calculated for [M(^{81}Br)-H$^+$] = 394,9894, found 394,9896

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ 9.04 (br. s, 1 H) 7.75 (d, *J*=8.48 Hz, 1 H) 7.28 - 7.42 (m, 1 H) 4.66 (dd, J=8,76, 5.75 Hz, 1 H) 3.63 (dd, J=14.32, 5.65 Hz, 1 H) 3.15 (dd, *J*=14.51, 8.85 Hz, 1 H) 2.59 – 2.78 (s, 3 H) ppm

^{13}C NMR: (75 MHz, CHLOROFORM-*d*) δ 172.24 (C=O) 136.43 (C) 134.04 (C) 130.39 (CH) 129.33 (CH) 128.66 (CH) 127.80 (C) 127.29 (C) 126.98 (CH) 124.04 (CH) 62.75 (CH) 36.21 (CH_2) 32.93(CH_3) ppm

TLC: R_f = 0,04 (hexane/EtOAc 90/10)

3.6.20 3-BENZYL-2,3-DIHYDRO-8-FLUORO-2-METHYL-1,2,5-BENZOTHIADIAZEPIN-4(5*H*)-ONE-1,1-DIOXIDE **II.7-S**



Formula: $C_{16}H_{15}FN_2O_3S$ (white solid)

Molecular weight: 334,37 g/mol

Yield: 24%

LC-MS:

t_{ret} = 16,1 min (Method A)
ES-MS [m/z (fragment, intensity)]: 333,0 (M-H$^+$, 100)
Purity: 94%

HR-MS (ESI): calculated for [M-H$^+$] = 333,0715, found 333,0725

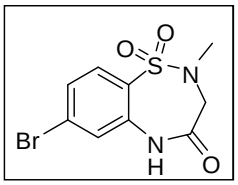
^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 10.55 (br. s., 1 H) 7.46 - 7.59 (m, 2 H) 7.16 - 7.41 (m, 4 H) 4.75 (dd, *J*=10.0, 4.9 Hz, 1 H) 3.39 (d, *J*=1.9 Hz, 1 H) 3.01 (dd, *J*=14.6, 9.9 Hz, 1 H) 2.63 (s, 3 H)

^{13}C NMR: (75 MHz, DMSO-d_6) δ 170.48 (C=O) 156.99 (d, *J*=244.80 Hz, C) 137.23 (C) 130.34 (d, *J*=6.59 Hz, C) 129.37 (CH) 128.10 (CH) 126.34 (CH) 124.26 (d, *J*=7.68 Hz, CH) 121.31 (d, *J*=22.50 Hz, CH) 114.12 (d, *J*=25.25 Hz, CH) 61.52 (CH) 34.79 (CH_2) 32.48 (CH_3) ppm

IR (HATR): 3225 (vw) 3101 (vw) 2997 (vw) 2362 (vw) 1681 (w) 1491 (m) 1456 (vw) 1403 (w) 1338 (w) 1270 (w) 1218 (w) 1162 (m) 830 (vw) 757 (w) 738 (w) 696 (w) 629 (w)

TLC: R_f = 0,22 (hexane/EtOAc 60/40)

3.6.21 7-BROMO-2,3-DIHYDRO-2-METHYL-1,2,5-BENZOTHIADIAZEPIN-4(5*H*)-ONE-1,1-DIOXIDE **II.7-T**



Formula: $C_9H_9BrN_2O_3S$ (white solid)

Molecular weight: 305,15 g/mol

Yield: 56%

LC-MS:
t_{ret} = 14,2 min (Method A)
ES-MS [m/z (fragment, intensity)]: 302,9 ((M(^{79}Br)-H^+, 50), 304,9 (M(^{81}Br)-H^+, 50)
Purity: 97%

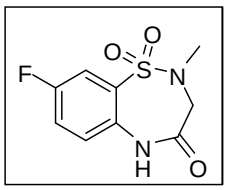
HR-MS (ESI): calculated for [M(^{81}Br)-H^+] = 304,9424, found 304,9427

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 10.70 (s, 1 H) 7.69 (d, *J*=8.5 Hz, 1 H) 7.61 (d, *J*=1.7 Hz, 1 H) 7.45 (dd, *J*=8.5, 1.9 Hz, 1 H) 4.26 (s, 2 H) 2.73 (s, 3 H)

^{13}C NMR: (75 MHz, DMSO-d_6) δ 170.45 (C=O) 136.07 (C) 130.25 (CH) 127.12 (C) 126.84 (C) 125.85 (CH) 123.67 (CH) 53.98 (CH_2) 36.02 (CH_3) ppm

TLC: R_f = 0,26 (hexane/EtOAc 60/40)

3.6.22 2,3-DIHYDRO-8-FLUORO-2-METHYL-1,2,5-BENZOTHIADIAZEPIN-4(5*H*)-ONE-1,1-DIOXIDE **II.7-U**



Formula: $C_9H_9FN_2O_3S$ (white solid)

Molecular weight: 244,24 g/mol

Yield: 61%

LC-MS:
t_{ret} = 13,0 min (Method A)
ES-MS [m/z (fragment, intensity)]: 243,0 (M-H^+, 100)
Purity: 96%

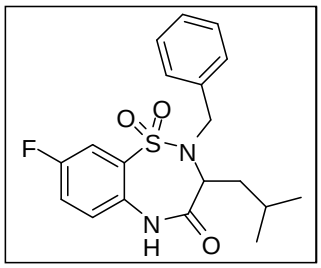
HR-MS (ESI): calculated for [M-H^+] = 243,0245, found 243,0256

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 10.63 (br. s., 1 H) 7.48 - 7.61 (m, 2 H) 7.35 - 7.47 (m, 1 H) 4.22 (s, 2 H) 2.74 (s, 3 H)

^{13}C NMR: (75 MHz, DMSO-d_6) δ 169.80 (C=O) 156.95 (d, *J*=244.80 Hz, C) 131.56 (C) 128.74 (C) 124.00 (d, *J*=6.58 Hz, CH) 121.60 (d, *J*=23.06 Hz, C) 114.47 (d, *J*=25.25 Hz, C) 54.08 (CH) 36.17 (CH_2) 32.93 (CH_3) ppm

TLC: R_f = 0,08 (hexane/EtOAc 60/40)

3.6.23 2-BENZYL-2,3-DIHYDRO-8-FLUORO-3-ISOBUTYL-1,2,5-BENZOTHIADIAZEPIN-4(5*H*)-ONE-1,1-DIOXIDE **II.7-V**



Formula: $C_{19}H_{21}FN_2O_3S$ (white solid)

Molecular weight: 376,45 g/mol

Yield: 46%

LC-MS:

t_{ret} = 18,2 min (Method A)

ES-MS [m/z (fragment, intensity)]: 375,0 ($M-H^+$, 100)

Purity: 98%

HR-MS (ESI): calculated for [$M-H^+$] = 375,1184, found 375,1181

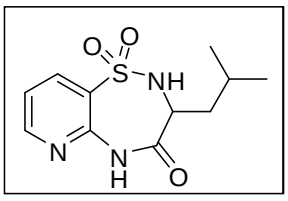
^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 8.26 (br. s., 1 H) 7.70 (dd, *J*=7.7, 2.8 Hz, 1 H) 7.27 - 7.41 (m, 3 H) 7.15 - 7.25 (m, 1 H) 6.96 (dd, *J*=8.9, 4.3 Hz, 1 H) 4.55 - 4.65 (m, 2 H) 4.11 (d, *J*=15.6 Hz, 1 H) 1.67 - 1.76 (m, 2 H) 1.59 - 1.67 (m, 1 H) 0.82 (d, *J*=6.4 Hz, 3 H) 0.60 (d, *J*=6.4 Hz, 3 H)

^{13}C NMR: (75 MHz, CHLOROFORM-*d*) δ 172.68 (C=O) 157.30 (d, *J*=250.29 Hz, C) 135.71 (C) 131.91 (d, *J*=6.58 Hz, C) 128.80 (C) 128.54 (CH) 128.49 (CH) 128.17 (CH) 123.10 (d, *J*=7.68 Hz, CH) 121.25 (d, *J*=23.05 Hz, CH) 115.64 (d, *J*=25.25 Hz, CH) 58.37 (CH) 50.42 (CH_2) 38.12 (CH_2) 23.59 (CH) 22.65 (CH_3) 12.38 (CH_3) ppm

IR (HATR): 3218 (vw) 3098 (w) 3001 (w) 2959 (w) 2868 (w) 2356 (vw) 1663 (m) 1593 (w) 1492 (m) 1457 (w) 1406 (m) 1366 (w) 1343 (m) 1305 (w) 1266 (w) 1209 (w) 1157 (m) 1082 (vw) 1040 (w) 1026 (w) 954 (w) 929 (vw) 905 (w) 863 (m) 840 (w) 806 (w) 762 (vw) 728 (w) 696 (m) 666 (w) 646 (vw)

TLC: R_f = 0,28 (hexane/EtOAc 60/40)

3.6.24 2,3-DIHYDRO-3-ISOBUTYL-[2,3-F]PYRIDINYL-1,2,5-BENZOTHIADIAZEPIN-4(5*H*)-ONE-1,1-DIOXIDE **II.7-W**



Formula: $C_{11}H_{15}N_3O_3S$ (white solid)

Molecular weight: 269,32 g/mol

Yield: 10%

LC-MS:

t_{ret} = 17,6 min (Method A)

ES-MS [m/z (fragment, intensity)]: 270,1 ($M+H^+$, 100)

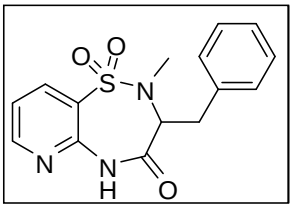
HR-MS (ESI): calculated for [$M-H^+$] = 268,0761, found 268,0767

^{1}H NMR (300 MHz, Acetone-d_6) δ ppm 8.49 - 8.61 (m, 1 H) 8.24 (dd, *J*=7.8, 1.6 Hz, 1 H) 7.46 (br. s., 1 H) 7.31 (dd, *J*=7.8, 4.6 Hz, 1 H) 4.37 (dd, *J*=10.5, 4.0 Hz, 1 H) 1.65 - 2.02 (m, 3 H) 0.98 (t, *J*=6.0 Hz, 6 H)

^{13}C NMR: (75 MHz, Acetone-d_6) δ 153.31 (CH) 138.00 (CH) 119.70 (CH) 55.17 (CH) 40.71 (CH_2) 24.73 (CH) 23.64 (CH_3) 21.21 (CH_3) ppm (quaternary signals not visible, not enough product)

TLC: R_f = 0,18 (hexane/EtOAc 60/40)

3.6.25 3-BENZYL-2,3-DIHYDRO-2-METHYL-[2,3-F]PYRIDINYL-1,2,5-BENZOTHIADIAZEPIN-4(5*H*)-ONE-1,1-DIOXIDE **II.7-X**



Formula: $C_{15}H_{215}N_3O_3S$ (white solid)

Molecular weight: 317,36 g/mol

Yield: 5%

LC-MS:

t_{ret} = 5,6 min (method C)

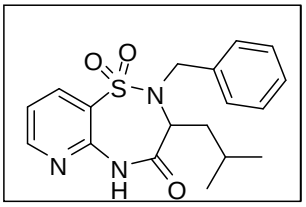
ES-MS [m/z (fragment, intensity)]: 318,0 ($M+H^+$, 70), 290,1 ($M+H^+$-28, 30)

HR-MS (ESI): calculated for [$M-H^+$] = 316,0761, found 316,0763

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ 8.71 (br. s., 1 H) 8.55 (dd, *J*=4.7, 1.7 Hz, 1 H) 8.24 (dd, *J*=7.8, 1.6 Hz, 1 H) 7.28 - 7.44 (m, 4 H) 7.19 (dd, *J*=7.9, 4.7 Hz, 2 H) 4.96 (dd, *J*=9.6, 5.3 Hz, 1 H) 3.65 (dd, *J*=14.8, 5.4 Hz, 1 H) 3.11 (dd, *J*=14.9, 9.6 Hz, 1 H) 2.79 (s, 3 H) ppm

TLC: R_f = 0,16 (hexane/EtOAc 60/40)

3.6.26 2-BENZYL-2,3-DIHYDRO-3-ISOBUTYL-[2,3-F]PYRIDINYL-1,2,5-BENZOTHIADIAZEPIN-4(5*H*)-ONE-1,1-DIOXIDE **II.7-Y**



Formula: $C_{18}H_{21}N_3O_3S$ (white solid)

Molecular weight: 359,44 g/mol

Yield: 18%

LC-MS:

t_{ret} = 17,6 min (Method A)

ES-MS [m/z (fragment, intensity)]: 360,1 ($M+H^+$, 100)

HR-MS (ESI): calculated for [$M-H^+$] = 358,1231, found 358,1238

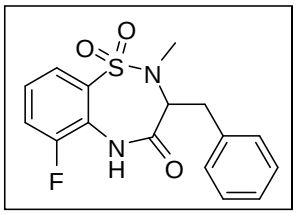
^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 10.71 (br. s., 1 H) 8.60 (d, *J*=3.2 Hz, 1 H) 8.32 (d, *J*=7.9 Hz, 1 H) 7.19 - 7.48 (m, 6 H) 4.71 (dd, *J*=9.8, 4.1 Hz, 1 H) 4.62 (d, *J*=16.0 Hz, 1 H) 3.99 (d, *J*=16.0 Hz, 1 H) 1.35 - 1.67 (m, 3 H) 0.73 (d, *J*=6.0 Hz, 3 H) 0.50 (d, *J*=6.2 Hz, 3 H)

^{13}C NMR: (75 MHz, DMSO-d_6) δ 171.47 (C=O) 152.78 (CH) 144.80 (C) 138.32 (CH) 137.03 (C) 128.34 (CH) 127.97 (CH) 127.63 (CH) 125.81 (C) 119.21 (CH) 58.43 (CH) 49.74 (CH_2) 37.67 (CH_2) 23.04 (CH) 22.69 (CH_3) 20.88 (CH_3) ppm

IR (HATR): 3136 (vw) 3061 (vw) 2958 (w) 2358 (m) 2342 (m) 1686 (w) 1579 (m) 1508 (w) 1447 (w) 1424 (w) 1327 (m) 1285 (w) 1207 (w) 1164 (m) 1146 (w) 1094 (w) 1052 (w) 1026 (w) 929 (vw) 869 (w) 804 (m) 780 (w) 770 (w) 756 (w) 730 (m) 697 (m) 668 (w) 647 (w)

TLC: R_f = 0,20 (hexane/EtOAc 60/40)

3.6.27 3-BENZYL-2,3-DIHYDRO-8-FLUORO-2-METHYL-1,2,5-BENZOTHIADIAZEPIN-4(5*H*)-ONE-1,1-DIOXIDE **II.7-Z**



Formula: $C_{16}H_{15}FN_2O_3S$ (white solid)

Molecular weight: 334,37 g/mol

Yield: 19%

LC-MS:

t_{ret} = 16,1 min (Method A)

ES-MS [m/z (fragment, intensity)]: 333,0 ($M\text{-}H^+$, 100)

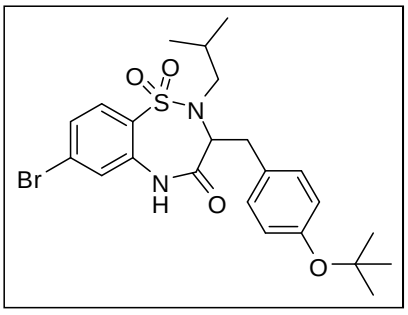
HR-MS (ESI): calculated for [$M\text{-}H^+$] = 333,0715, found 333,0712

^{1}H NMR: (500 MHz, CHLOROFORM-*d*) δ ppm 7.84 (d, *J*=5.5 Hz, 1 H) 7.70 (dt, *J*=8.1, 1.3 Hz, 1 H) 7.27 - 7.35 (m, 5 H) 7.18 (td, *J*=8.1, 5.0 Hz, 1 H) 4.77 (dt, *J*=9.4, 5.2 Hz, 1 H) 3.63 (dd, *J*=14.7, 5.5 Hz, 1 H) 3.13 (dd, *J*=14.6, 9.4 Hz, 1 H) 2.75 (d, *J*=0.9 Hz, 3 H)

^{13}C NMR: (125 MHz, CHLOROFORM-*d*) δ 170.61 (C=O) 136.26 (C) 129.28 (CH) 128.65 (CH) 127.00 (CH) 124.59 en 124.56 (d, *J*=3.63 Hz, CH) 124.12 (d, *J*=8.18 Hz, CH) 122.10 (C) 119.25 (d, *J*=21.8 Hz, C) 61.85 (d, *J*=8.17 Hz, CH) 35.57 (d, *J*=7.27 Hz, CH_2) 32.16 (d, *J*=6.36 Hz, CH_3) ppm (quaternal signals on F-substituted benzene are not visible)

TLC: R_f = 0,07 (hexane/EtOAc 80/20)

3.6.28 7-BROMO-3-(4-*TERT*-BUTOXYBENZYL)-2,3-DIHYDRO-2-ISOBUTYL-1,2,5-BENZOTHIADIAZEPIN-4(5*H*)-ONE-1,1-DIOXIDE **II.7-AA**



Formula: $C_{23}H_{29}BrN_2O_4S$ (white solid)

Molecular weight: 509,46 g/mol

Yield: 23%

LC-MS:

t_{ret} = 19,6 min (Method A)

ES-MS [m/z (fragment, intensity)]: 507,1 (($M(^{79}Br)\text{-}H^+$, 50), 509,1 ($M(^{81}Br)\text{-}H^+$, 50)

Purity: 98%

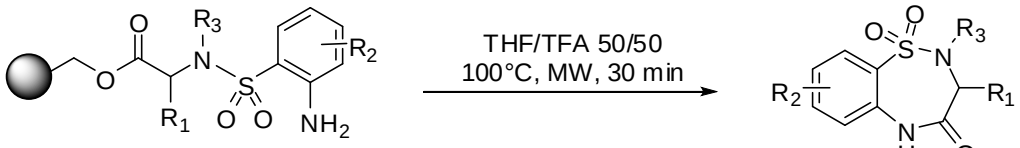
HR-MS (ESI): calculated for [$M(^{81}Br)\text{-}H^+$] = 509,0938, found 509,0949

^{1}H NMR (500 MHz, acetone-d_6) δ ppm 9.50 (s, 1 H) 7.72 (d, *J*=8.4 Hz, 1 H) 7.62 (d, *J*=1.7 Hz, 1 H) 7.42 (dd, *J*=8.4, 1.8 Hz, 1 H) 7.29 (d, *J*=8.4 Hz, 2 H) 6.91 - 6.99 (m, 2 H) 4.52 (dd, *J*=9.7, 5.0 Hz, 1 H) 3.60 (dd, *J*=14.1, 5.0 Hz, 1 H) 3.30 (dd, *J*=14.2, 9.8 Hz, 1 H) 2.79 (d, *J*=4.9 Hz, 1 H) 2.48 (dd, *J*=14.1, 9.7 Hz, 1 H) 1.36 - 1.48 (m, 2 H) 1.24 - 1.35 (m, 10 H) 0.62 (d, *J*=6.6 Hz, 3 H) 0.55 (d, *J*=6.5 Hz, 3 H)

^{13}C NMR: (125 MHz, acetone-d_6) δ 172.84 (C=O) 155.31 (C) 137.71 (C) 133.73 (C) 131.35 (CH) 130.82 (CH) 129.97 (C) 127.88 (C) 126.77 (CH) 125.00 (CH) 124.56 (CH) 78.56 (C) 67.16 (CH) 58.48 (CH_2) 39.39 (CH_2) 29.20 (CH_3) 27.93 (CH) 20.26 (CH_3) ppm

TLC: R_f = 0,04 (hexane/EtOAc 90/10)

3.7 RING CLOSURE IN ACIDIC CONDITIONS

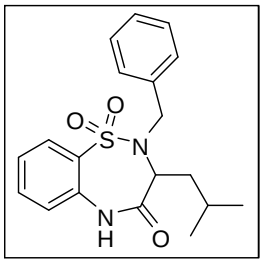


II.27 **II.7**

3.7.1 GENERAL PROCEDURE

To ring closing precursor **II.27** (0.18 mmol, 1 eq), brought in a microwave tube, is added 3 ml of a 50/50 mixture of THF in TFA. This suspension is heated to 100°C for 30 min using microwave irradiation and applying constant cooling (Powermax method). The resin is subsequently filtered off, washed with some THF and the filtrate evaporated under reduced pressure. The crude product is purified using column chromatography or recrystallization, yielding the desired benzothiadiazepinones **II.7**.

3.7.2 2-BENZYL-2,3-DIHYDRO-3-ISOBUTYL-1,2,5-BENZOTHIADIAZEPIN-4(5*H*)-ONE-1,1-DIOXIDE **II.7-AB**



Formula: $C_{19}H_{22}N_2O_3S$ (white solid)

Molecular weight: 358,45 g/mol

Yield: 12%

LC-MS:
t_{ret} = 6,6 min (Method C)
ES-MS [m/z (fragment, intensity)]: 357,1 ($M-H^+$, 100)
purity: 97%

HR-MS (ESI): calculated for [$M-H^+$] = 357,1278, found 357,1289

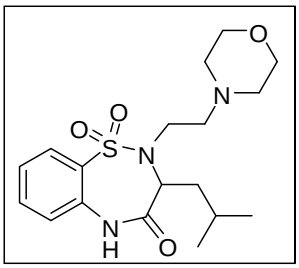
^{1}H NMR: (300 MHz, Acetone-d_6) δ ppm 9.38 (br. s., 1 H) 7.92 (dd, *J*=8.0, 1.2 Hz, 1 H) 7.54 - 7.67 (m, 1 H) 7.22 - 7.50 (m, 7 H) 4.55 - 4.71 (m, 2 H) 4.08 (d, *J*=15.8 Hz, 1 H) 1.48 - 1.78 (m, 3 H) 0.77 (d, *J*=6.2 Hz, 3 H) 0.55 (d, *J*=6.2 Hz, 3 H)

^{13}C NMR: (75 MHz, Acetone-*d*$_6$) δ 172.81 (C=O) 138.40 (C) 134.65 (C) 134.48 (CH) 131.38 (C) 129.68 (CH) 129.31 (CH) 128.61 (CH) 124.49 (CH) 122.68 (CH) 122.60 (CH) 59.49 (CH) 51.09 (CH_2) 39.43 (CH_2) 24.39 (CH_3) 23.16 (CH_3) 21.50 (CH) ppm

IR (HATR): 3127 (vw) 2952 (w) 1683 (m) 1597 (w) 1586 (w) 1480 (w) 1429 (w) 1367 (w) 1340 (w) 1225 (vw) 1157 (m) 1142 (w) 1078 (vw) 1041 (w) 924 (vw) 870 (w) 798 (w) 748 (w) 733 (w) 696 (w) 653 (w) 618 (w)

TLC: R_f = 0,08 (hexane/EtOAc 80/20)

3.7.3 2,3-DIHYDRO-3-ISOBUTYL-2-(N-MORPHOLINOETHYL)-1,2,5-BENZOTHIADIAZEPIN-4(5*H*)-ONE-1,1-DIOXIDE **II.7-AC**



Formula: $C_{18}H_{27}N_3O_4S$ (white solid)

Molecular weight: 381,49 g/mol

Yield: 10%

LC-MS:
t_{ret} = 16,5 min (Method A)
ES-MS [m/z (fragment, intensity)]: 380,1 ($M-H^+$, 100)
purity: 90%

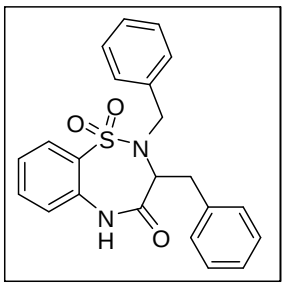
HR-MS (ESI): calculated for [$M-H^+$] = 380,1650, found 380,1660

^{1}H NMR (300 MHz, Acetone-*d*$_6$) δ ppm 9.40 (br. s., 1 H) 7.87 (d, *J*=7.9 Hz, 1 H) 7.61 (t, *J*=7.7 Hz, 1 H) 7.39 (d, *J*=8.1 Hz, 1 H) 7.31 (t, *J*=7.6 Hz, 1 H) 4.60 (d, *J*=7.5 Hz, 1 H) 3.91 (br. s., 4 H) 3.74 - 3.84 (m, 1 H) 3.46 (br. s., 6 H) 1.84 (br. s., 4 H) 0.98 (dd, *J*=15.6, 4.3 Hz, 6 H)

^{13}C NMR: (75 MHz, Acetone-*d*$_6$) δ 172.09 (C=O) 134.78 (CH) 134.36 (C) 130.19 (C) 129.71 (CH) 124.75 (CH) 122.77 (CH) 64.66 (CH_2) 59.14 (CH) 57.27 (CH_2) 52.98 (CH_2) 41.19 (CH_2) 38.66 (CH_2) 24.87 (CH) 23.45 (CH_3) 21.77 (CH_3) ppm

TLC: R_f = 0,10 (CH_2Cl_2/MeOH 97/3)

3.7.4 2,3-DIHYDRO-2,3-BENZYL-2-METHYL-1,2,5-BENZOTHIADIAZEPIN-4(5*H*)-ONE-1,1-DIOXIDE **II.7-AD**



Formula: $C_{22}H_{20}N_2O_3S$ (white solid)

Molecular weight: 392,47 g/mol

Yield: 22%

LC-MS:
t_{ret} = 17,8 min (Method A)
ES-MS [m/z (fragment, intensity)]: 391,1 ($M-H^+$, 100)
Purity: 95%

HR-MS (ESI): calculated for [M-H$^+$] = 391,1116, found 391,1114

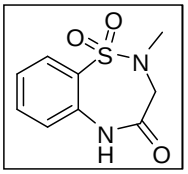
^{1}H NMR: (300 MHz, CHLOROFORM-*d*) δ ppm 8.84 (d, *J*=10.2 Hz, 1 H) 7.94 (d, *J*=7.9 Hz, 1 H) 7.50 (t, *J*=7.5 Hz, 1 H) 7.06 - 7.28 (m, 9 H) 7.00 (d, *J*=7.5 Hz, 1 H) 6.78 - 6.91 (m, 2 H) 4.44 - 4.58 (m, 1 H) 4.27 (dd, *J*=14.7, 4.5 Hz, 1 H) 3.80 (dd, *J*=15.1, 3.6 Hz, 1 H) 3.48 - 3.63 (m, 1 H) 3.19 - 3.37 (m, 1 H)

^{13}C NMR: (75 MHz, CHLOROFORM-*d*) δ 172.81 (C=O) 137.27 (C) 134.38 (C) 134.06 (C) 133.69 (CH) 130.80 (C) 129.59 (CH) 128.73 (CH) 128.56 (CH) 128.46 (CH) 128.23 (CH) 128.09 (CH) 126.62 (CH) 123.87 (CH) 121.03 (CH) 63.25 (CH) 52.66 (CH_2) 38.81(CH_2) ppm

IR (HATR): 3220 (w) 3031 (w) 2360 (w) 2342 (w) 1665 (m) 1594 (w) 1582 (w) 1477 (w) 1453 (w) 1431 (w) 1382 (w) 1346 (m) 1306 (w) 1194 (w) 1171 (m) 1138 (w) 1089 (w) 1055 (vw) 1018 (w) 938 (vw) 871 (w) 795 (w) 765 (w) 732 (w) 717 (w) 692 (m) 668 (w) 632 (vw)

TLC: R_f = 0,22 (hexane/EtOAc 75/25)

3.7.5 2,3-DIHYDRO-2-METHYL-1,2,5-BENZOTHIADIAZEPIN-4(5*H*)-ONE-1,1-DIOXIDE **II.7-AE**



Formula: $C_9H_{10}N_2O_3S$ (white solid)

Molecular weight: 226,25 g/mol

Yield: 42%

LC-MS:
t_{ret} = 12,4 min (Method A)
ES-MS [m/z (fragment, intensity)]: 225,0 (M-H$^+$, 100)

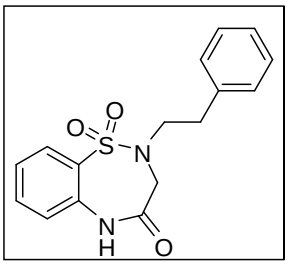
HR-MS (ESI): calculated for [M-H$^+$] = 225,0334, found 225,0339

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 8.77 (br. s., 1 H) 7.89 (dd, *J*=7.9, 1.5 Hz, 1 H) 7.47 (td, *J*=7.5, 1.5 Hz, 1 H) 7.17 (m, 1 H) 7.03 (d, *J*=8.3 Hz, 1 H) 4.30 (s, 2 H) 2.78 (s, 3 H)

^{13}C NMR: (75 MHz, CHLOROFORM-*d*) δ 171.52 (C=O) 134.14 (CH) 133.38 (C) 129.58 (CH) 128.56 (C) 124.10 (CH) 121.14 (CH) 54.31 (CH_2) 36.31 (CH_3) ppm

TLC: R_f = 0,09 (CH_2Cl_2)

3.7.6 2,3-DIHYDRO-2-PHENYLETHYL-1,2,5-BENZOTHIADIAZEPIN-4(5*H*)-ONE-1,1-DIOXIDE **II.7-AF**



Formula: $C_{16}H_{16}N_2O_3S$ (white solid)

Molecular weight: 316,37 g/mol

Yield: 47%

LC-MS:
t_{ret} = 15,8 min (Method A)
ES-MS [m/z (fragment, intensity)]: 315,0 ($M\text{-}H^+$, 100)

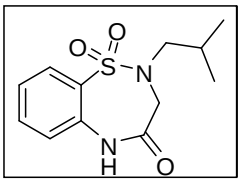
HR-MS (ESI): calculated for [$M\text{-}H^+$] = 315,0803, found 315,0804

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 9.22 (br. s., 3 H) 7.94 (dd, *J*=7.9, 1.3 Hz, 4 H) 7.50 (t, *J*=7.7 Hz, 5 H) 7.27 - 7.34 (m, 5 H) 7.04 - 7.24 (m, 24 H) 4.28 (s, 9 H) 3.29 (t, *J*=7.4 Hz, 9 H) 2.91 (t, *J*=7.4 Hz, 9 H)

^{13}C NMR: (75 MHz, CHLOROFORM-*d*) δ 172.06 (C=O) 137.32 (C) 133.99 (CH) 133.60 (C) 129.94 (C) 129.01 (CH) 128.78 (CH) 126.89 (CH) 123.79 (CH) 121.21 (CH) 52.33 (CH_2) 50.61 (CH_2) 35.23 (CH_2) ppm

TLC: R_f = 0,06 (hexane/EtOAc 80/20)

3.7.7 2,3-DIHYDRO-2-ISOBUTYL-1,2,5-BENZOTHIADIAZEPIN-4(5*H*)-ONE-1,1-DIOXIDE **II.7-AG**



Formula: $C_{12}H_{16}N_2O_3S$ (white solid)

Molecular weight: 268,33 g/mol

Yield: 32%

LC-MS:
t_{ret} = 15,1 min (Method A)
ES-MS [m/z (fragment, intensity)]: 267,0 ($M\text{-}H^+$, 100)

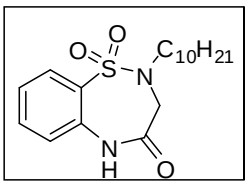
HR-MS (ESI): calculated for [$M\text{-}H^+$] = 267,0803, found 267,0806

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 8.62 (br. s., 1 H) 7.95 (dd, *J*=7.9, 1.3 Hz, 1 H) 7.52 (t, *J*=7.8 Hz, 1 H) 7.17 - 7.24 (m, 1 H) 7.06 (d, *J*=7.9 Hz, 1 H) 4.38 (s, 2 H) 2.76 (d, *J*=7.3 Hz, 2 H) 1.93 (m, *J*=13.7 Hz, 1 H) 0.94 (d, *J*=6.8 Hz, 6 H)

^{13}C NMR: (75 MHz, CHLOROFORM-*d*) δ 171,64 (C=O) 133.93 (CH) 133.42 (C) 129.77 (C) 129.34 (CH) 123.80 (CH) 120.99 (CH) 55.90 (CH_2) 51.95 (CH_2) 27.20 (CH) 19.78 (CH_3) ppm

TLC: R_f = 0,04 (hexane/EtOAc 80/20)

3.7.8 2-DECYL-2,3-DIHYDRO-1,2,5-BENZOTHIADIAZEPIN-4(5*H*)-ONE-1,1-DIOXIDE **II.7-AH**



Formula: $C_{17}H_{26}N_2O_3S$ (white solid)

Molecular weight: 352,49 g/mol

Yield: 10%

LC-MS:
t_{ret} = 10,3 min (method C)
ES-MS [m/z (fragment, intensity)]: 351,1 ($M-H^+$, 100)

HR-MS (ESI): calculated for [M(^{81}Br)-H^+] = 351,1748, found 351,1761

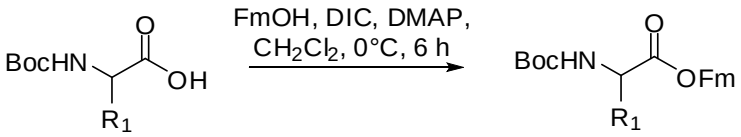
^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 8.47 (br. s., 1 H) 7.95 (dd, *J*=8.0, 1.4 Hz, 1 H) 7.52 (t, *J*=7.9 Hz, 1 H) 7.17 - 7.23 (m, 1 H) 7.02 (d, *J*=8.1 Hz, 1 H) 4.38 (s, 2 H) 3.03 (t, *J*=7.3 Hz, 2 H) 1.50 - 1.65 (m, 2 H) 1.24 (br. s., 14 H) 0.87 (t, *J*=6.4 Hz, 3 H)

^{13}C NMR: (75 MHz, CHLOROFORM-*d*) δ 171.62 (C=O) 133.91 (CH) 133.45 (C) 129.96 (C) 129.21 (CH) 123.82 (CH) 120.92 (CH) 51.26 (CH_2) 48.71 (CH_2) 31.83 (CH_2) 29.44 (CH_2) 29.24 (CH_2) 29.05 (CH_2) 27.84 (CH_2) 26.33 (CH_2) 22.64 (CH_2) 14.07 (CH_3) ppm

TLC: R_f = 0,07 (hexane/EtOAc 75/25)

4 2,3-DIHYDRO-1,2,5-BENZOTHIADIAZEPIN-4(5*H*)-ONE-1,1-DIOXIDES VIA THE ON-RESIN CYCLIZATION STRATEGY

4.1 SYNTHESIS OF THE α-AMINO ACID FLUORENYLMETHYL ESTERS **II.94**

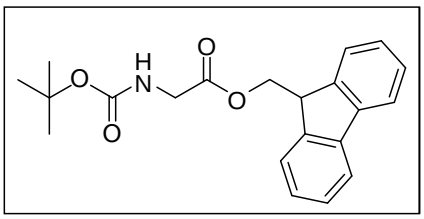


II.51 **II.52**

4.1.1 GENERAL PROCEDURE

To a stirred solution of the Boc-protected α-amino acid **II.51** (33.9 mmol, 1 eq) in 225 ml CH_2Cl_2 at 0°C, is added fluorenylmethanol (6.65 g, 33.9 mmol, 1 eq) and DMAP (0.83 g, 6.77 mmol, 0.2 eq). Subsequently, DIC (5.25 ml, 33.9 mmol, 1 eq) is added dropwise to this reaction mixture and the reaction is allowed to stir further for 6 h. The ureum precipitate is filtered and washed with some CH_2Cl_2, followed by evaporation of the filtrate under reduced pressure. This crude mixture is then purified by column chromatography.

4.1.2 N-(*TERT*-BUTOXYCARBONYL)-L-GLYCINE FLUORENYLMETHYL ESTER **II.94-A**



Eluent: hexane/ethyl acetate 95/5

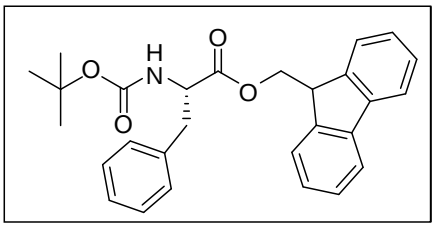
Yield: 60% (white solid)

Formula: $C_{21}H_{23}NO_4$

Molecular weight: 353,41 g/mol

TLC: R_f = 0,25 (hexane/EtOAc 80/20)

4.1.3 N-(*TERT*-BUTOXYCARBONYL)-L-PHENYLALANINE FLUORENYLMETHYL ESTER **II.94-B**



Eluent: isooctane/ethyl acetate 95/5

Yield: 73% (white solid)

Formula: $C_{28}H_{29}NO_4$

Molecular weight: 443,53 g/mol

LC-MS:

t_{ret} = 20,5 min (Method A)

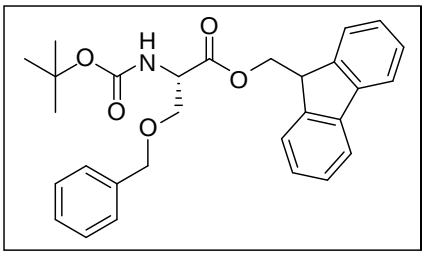
ES-MS [m/z (fragment, intensity)]: 344.1 ($M+H^+$-Boc, 100), 179,1 (dibenzofulvene + H^+, 40) 166,1 ($M+H^+$-Boc-dibenzofulvene, 40)

^{1}H NMR (300 MHz, DICHLOROMETHANE-d_2) δ ppm 7.79 (d, *J*=7.3 Hz, 2 H) 7.58 (t, *J*=6.7 Hz, 2 H) 7.19 - 7.51 (m, 7 H) 7.10 (d, *J*=6.6 Hz, 2 H) 4.95 (d, *J*=7.3 Hz, 1 H) 4.58 (d, *J*=6.2 Hz, 1 H) 4.43 (d, *J*=6.8 Hz, 2 H) 4.20 (t, *J*=6.6 Hz, 1 H) 2.83 - 3.14 (m, 2 H) 1.40 (s, 9 H)

^{13}C NMR: (75 MHz, DICHLOROMETHANE-d_2) 172.41 (C=O), 144.27 (C), 141.90 (C), 136.89 (C), 129.89 (CH), 129.08 (CH), 128.42 (CH), 127.76 (CH), 127.54 (CH), 125.61 (CH), 120.56 (CH), 67.56 (CH_2), 47.39 (CH), 38.70 (CH_2), 28.59 (CH)

TLC: R_f = 0.42 (isooctane/EtOAc 70/30)

4.1.4 N-(*TERT*-BUTOXYCARBONYL)-O-BENZYL-L-SERINE FLUORENYLMETHYL ESTER **II.94-C**



Eluent: hexane/ethyl acetate 95/5

Yield: 86% (white solid)

Formula: $C_{29}H_{31}NO_5$

Molecular weight: 473,56 g/mol

LC-MS:
t_{ret} = 7,6 min (method C)
ES-MS [m/z (fragment, intensity)]: 374,1 ($M+H^+$-Boc, 100), 179,1 (dibenzofulvene+H+, 10) 166,1 ($M+H^+$-Boc-dibenzofulveen, 10)

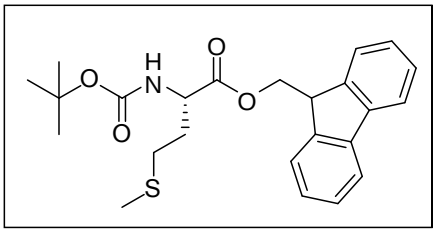
^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 7.73 - 7.83 (m, 2 H) 7.54 - 7.67 (m, 2 H) 7.22 - 7.46 (m, 9 H) 5.43 (d, *J*=8.9 Hz, 1 H) 4.37 - 4.61 (m, 4 H) 4.02 - 4.30 (m, 2 H) 3.79 - 3.94 (m, 1 H) 3.70 (dd, *J*=9.4, 3.2 Hz, 1 H) 1.37 - 1.52 (m, 9 H)

^{13}C NMR: (75 MHz, CHLOROFORM-*d*) 170.70 (C=O), 155.48 (C=O), 143.53 (C), 141.28 (C), 137.48 (C), 128.41 (CH), 127.81 (CH), 127.57 (CH), 127.16 (CH), 127.07 (CH), 125.01 (CH), 120.01 (CH), 80.05 (C), 73.30 (CH_2), 67.36 (CH_2), 61.48 (CH_2), 54.10 (CH), 46.74 (CH), 28.33 (CH_3)

TLC: R_f = 0,18 (hexane/EtOAc 80/20)

Optical rotation: $[\alpha]_D^{20}$ = -5° (c = 0.5, $CHCl_3$)

4.1.5 N-(*TERT*-BUTOXYCARBONYL)-L-METHIONINE FLUORENYLMETHYL ESTER **II.94-D**



Eluent: hexane/ethyl acetate 95/5

Yield: 53% (white solid)

Formula: $C_{24}H_{29}NO_4S$

Molecular weight: 427,55 g/mol

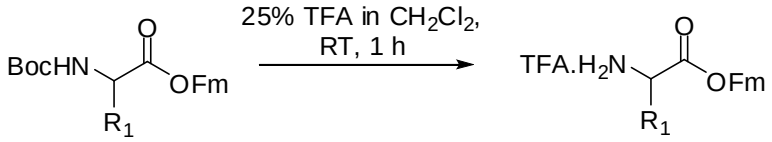
^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 7.78 (d, *J*=7.3 Hz, 2 H) 7.57 - 7.64 (m, 2 H) 7.38 - 7.47 (m, 2 H) 7.30 - 7.38 (m, 2 H) 5.06 (br. s., 1 H) 4.39 - 4.63 (m, 3 H) 4.24 (t, *J*=6.4 Hz, 1 H) 2.38 - 2.47 (m, 2 H) 2.05 (s, 3 H) 2.00 (d, *J*=8.3 Hz, 1 H) 1.71 - 1.90 (m, 1 H) 1.45 (s, 9 H)

^{13}C NMR: (75 MHz, CHLOROFORM-*d*) 172.26 (C=O) 143.50 (C) 143.28 (C) 141.38 (C) 127.90 (CH) 127.21 (CH) 124.94 (CH) 120.08 (CH) 66.90 (CH_2) 52.73 (CH) 46.84 (CH) 32.01 (CH_2) 29.81 (CH_2) 28.30 (CH_3) 15.36 (CH_3)

TLC: R_f = 0,30 (hexane/EtOAc 80/20)

Optical rotation: $[\alpha]_D^{20}$ = -4° (c = 0.5, $CHCl_3$)

4.2 SYNTHESIS OF THE TFA SALTS OF THE α-AMINO ACID FLUORENYLMETHYL ESTERS **II.80**

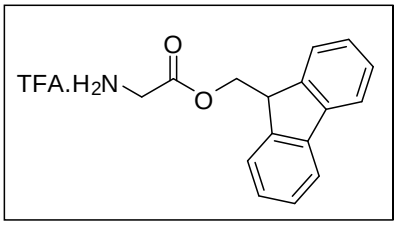


II.52 **II.53**

4.2.1 GENERAL PROCEDURE

The double protected α-amino acid **II.52** (13.7 g, 28.9 mmol, 1 eq) is brought in a flask, followed by the addition of 50 ml of a 25% solution of TFA in CH_2Cl_2. After stirring this reaction mixture for 1 h at room temperature, it is evaporated under reduced pressure and 50 ml of Et_2O is added to the crude product. The formed white precipitate is filtered off and washed with ether, yielding the desired α-amino acid ester salts **II.53**. If the filtrate is still turbid, this crystallization process is repeated a second time.

4.2.2 L-GLYCINE FLUORENYLMETHYL ESTER TRIFLUOROACETIC SALT **II.80-A**



Yield: 91% (white solid)

Formula: $C_{18}H_{16}F_3NO_4$

Molecular weight: 367,32 g/mol

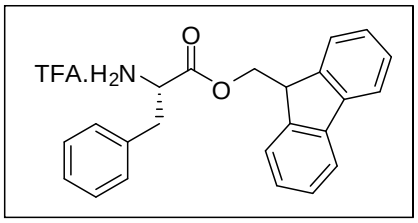
LC-MS:

t_{ret} = 5,7 min (method C)
ES-MS [m/z (fragment, intensity)]: 245,1 ($M+H^+$, 15), 179,1 (dibenzofulvene+H^+, 85)

^{1}H NMR (300 MHz, METHANOL-d_4) δ ppm 7.83 (d, *J*=7.5 Hz, 2 H) 7.65 (dd, *J*=7.4, 0.8 Hz, 2 H) 7.43 (t, *J*=7.5 Hz, 2 H) 7.34 (td, *J*=7.5, 1.3 Hz, 2 H) 4.63 (d, *J*=6.4 Hz, 2 H) 4.30 (t, *J*=6.4 Hz, 1 H) 3.86 (s, 2 H)

^{13}C NMR: (75 MHz, METHANOL-d_4) δ ppm 168.89 (OC=O) 144.82 (C) 142.79 (C) 129.19 (CH) 128.46 (CH) 126.13 (CH) 121.24 (CH) 68.90 (CH_2) 47.96 (CH) 41.03 (CH_2)

4.2.3 L-PHENYLALANINE FLUORENYLMETHYL TRIFLUOROACETIC SALT **II.80-B**



Yield: 90% (white solid)

Formula: $C_{25}H_{22}F_3NO_4$

Molecular weight: 457,44 g/mol

LC-MS:

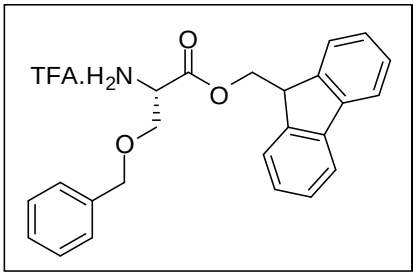
t_{ret} = 6,8 min (method C)
ES-MS [m/z (fragment, intensity)]: 344,1 ($M+H^+$, 65), 179,1 (dibenzofulvene+H^+, 20), 166,1 ($M+H^+$-dibenzofulvene, 15)

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 8.49 (br. s., 3 H) 7.82 - 7.96 (m, 2 H) 7.64 (d, *J*=7.3 Hz, 1 H) 7.53 (d, *J*=7.5 Hz, 1 H) 7.38 - 7.48 (m, 2 H) 7.20 - 7.38 (m, 5 H) 7.06 - 7.19 (m, 2 H) 4.54 - 4.70 (m, 1 H) 4.30 - 4.49 (m, 2 H) 4.17 (br. s., 1 H) 2.94 (br. s., 2 H)

^{13}C NMR: (75 MHz, METHANOL-d_4) δ ppm 170.40 (OC=O) 144.80 (C) 142.92 (C) 142.83 (C) 135.35 (C) 130.46 (CH) 130.34 (CH) 129.19 (CH) 129.12 (CH) 128.56 (CH) 128.48 (CH) 126.19 (CH) 125.97 (CH) 121.20 (CH) 68.69 (CH_2) 55.16 (CH) 48.12 (CH) 37.40 (CH_2)

Optical rotation: $[\alpha]_D^{20}$ = -45° (c = 1.05, methanol)

4.2.4 L-PHENYLALANINE FLUORENYLMETHYL ESTER TRIFLUOROACETIC SALT **II.80-C**



Yield: 64% (white solid)

Formula: $C_{26}H_{24}F_3NO_5$

Molecular weight: 487,47 g/mol

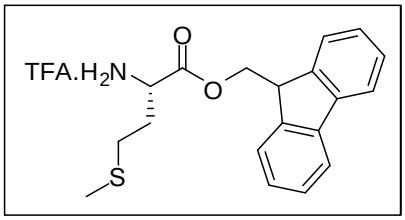
LC-MS:
t_{ret} = 6,8 min (method C)
ES-MS [m/z (fragment, intensity)]: 374,1 ($M+H^+$, 80), 179,1 (dibenzofulvene+H^+, 10), 196,1 ($M+H^+$-dibenzofulvene, 10)

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 7.60 - 7.68 (m, 2 H) 7.24 - 7.42 (m, 4 H) 7.07 - 7.18 (m, 7 H) 4.30 - 4.45 (m, 3 H) 4.01 - 4.12 (m, 2 H) 3.56 - 3.76 (m, 2 H)

^{13}C NMR: (75 MHz, METHANOL-d_4) δ ppm 168.76 (C) 144.88 (C) 144.71 (C) 142.89 (C) 142.78 (C) 138.46 (C) 129.69 (CH) 129.26 (CH) 129.19 (CH) 129.17 (CH) 128.51 (CH) 128.48 (CH) 125.99 (CH) 125.95 (CH) 121.24 (CH) 74.56 (CH_2) 68.74 (CH_2) 67.94 (CH_2) 54.41 (CH) 48.11 (CH)

Optical rotation: $[\alpha]_D^{20}$ = -14,5 ° (c = 1.05, methanol)

4.2.5 L-METHIONINE FLUORENYLMETHYL ESTER TRIFLUOROACETIC SALT **II.80-D**



Yield: 83% (white solid)

Formula: $C_{21}H_{22}F_3NO_4S$

Molecular weight: 441,46 g/mol

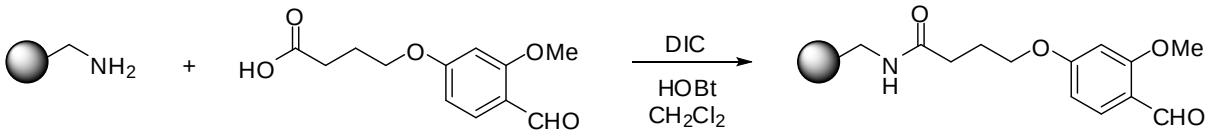
LC-MS:
t_{ret} = 6,4 min (method C)
ES-MS [m/z (fragment, intensity)]: 328,1 ($M+H^+$, 100), 179,1 (dibenzofulvene+H^+, 30), 150,1 ($M+H^+$-dibenzofulvene, 20)

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 7.74 (dd, *J*=7.5, 2.1 Hz, 2 H) 7.51 (t, *J*=6.7 Hz, 2 H) 7.39 (td, *J*=7.4, 3.7 Hz, 2 H) 7.28 - 7.35 (m, 2 H) 4.63 - 4.73 (m, 1 H) 4.50 - 4.60 (m, 1 H) 4.19 (t, *J*=5.7 Hz, 1 H) 4.09 (t, *J*=6.1 Hz, 1 H) 2.25 - 2.45 (m, 2 H) 1.88 - 2.03 (m, 5 H)

^{13}C NMR: (75 MHz, CHLOROFORM-*d*) δ ppm 170.69 (C=O) 145.03 (C) 144.61 (C) 143.10 (C) 142.91 (C) 129.25 (CH) 129.15 (CH) 128.55 (CH) 128.46 (CH) 125.92 (CH) 125.77 (CH) 121.34 (CH) 121.31 (CH) 67.98 (CH_2) 52.42 (CH) 48.29 (CH) 30.59 (CH_2) 29.87 (CH_2) 14.87(CH_3)

Optical rotation: $[\alpha]_D^{20}$ = -13° (c = 1.05, methanol)

4.3 SYNTHESIS OF FMPB-RESIN **II.99**



II.97; AM-PS **II.98**; FMPB-linker **II.99**

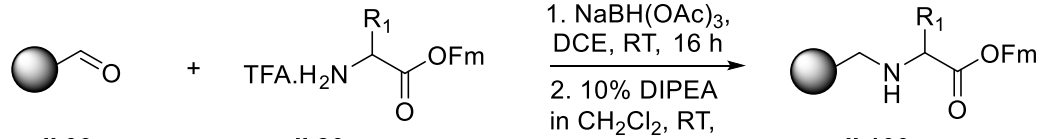
Preswell: The aminomethyl-polystyrene (2.00 g, 1.95 mmol, 1 eq) is preswollen by shaking it 2x 20 min in 30 ml CH_2Cl_2.

Preactivation: To a flask filled with 25 ml CH_2Cl_2 is added subsequently 4-(4-formyl-3-methoxyphenoxy)butyric acid (3.00 g, 12.0 mmol, 2 eq) and HOBt (1.62 g, 12.0 mmol, 2 eq). While this suspension is being stirred, DMF is added until all reagents are dissolved. Subsequently, DIC (1.86 ml, 12.0 mmol, 2 eq) is added to this yellow reaction mixture and stirred further for 30 min at room temperature.

Coupling: The obtained preactivated suspension is added in one portion to the resin and shaken for 8 h at room temperature. Then, the bright orange colored resin is filtered off and washed 3x with DMF, MeOH and CH_2Cl_2, delivering the desired FMPB resin **II.99**.

A chloranil color test was negative after coupling, confirming the total conversion towards the FMPB-resin **II.99**.

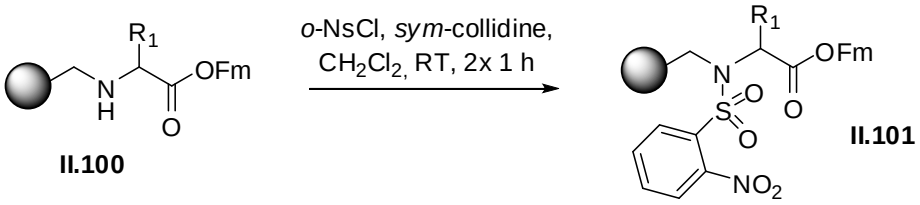
4.4 α-AMINO ACID COUPLING



II.99 **II.80** **II.100**

The FMPB resin **II.99** (0.500 g, 0.44 mmol, 1 eq) is preswollen 2x 20 min in 10 ml of CH_2Cl_2. Subsequently, 10 ml of 1,2-dichloroethane, α-amino acid **II.80** (0.484 g, 1.32 mmol, 3 eq) and $NaBH(OAc)_3$ (0.420 g, 1.98 mmol, 4.5 eq) are added to the FMPB-resin and this suspension is shaken for 16 h. The resin is then washed 3x with DMF, MeOH and CH_2Cl_2. To remove the TFA from the resin after coupling, the resin was shaken 2x 1 h in the presence of a 10% DIPEA solution in CH_2Cl_2 and washed 3x again with DMF, MeOH and CH_2Cl_2.

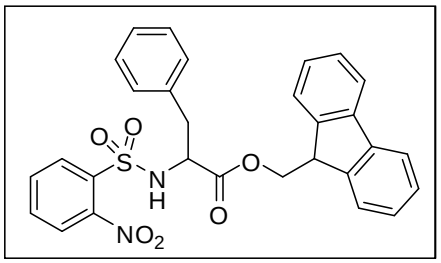
4.5 COUPLING OF *ORTHO*-NOSYL CHLORIDE



II.100 **II.101**

To the solid supported α-amino acid **II.100** (0.44 mol, 1 eq), suspended in 8 ml CH_2Cl_2, is consecutively added *sym*-collidine (0.292 ml, 2.20 mmol, 5 eq) and *o*-nosyl chloride (1.10 mmol, 2.5 eq). This suspension is shaken for 1 h at room temperature and washed 3x with DMF, MeOH and CH_2Cl_2. Then this coupling procedure is repeated for a second time, yielding the solid supported nosyl protected α-amino acid **II.101**.

This reaction was optimized for compound **II.101-a**, with R_1 = Bn and R_2 = H. LC-MS analysis after cleavage from the solid support delivered the following result:



Formula: $C_{29}H_{24}N_2O_6S$

Molecular weight: 528,58 g/mol

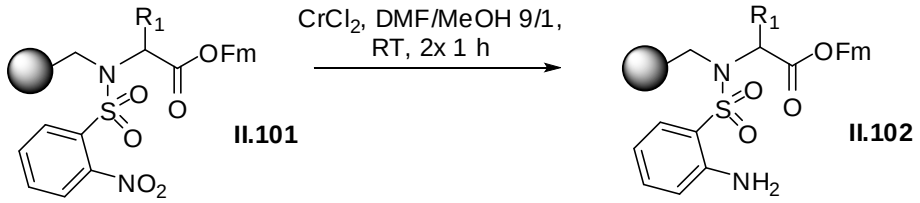
LC-MS:

purity: 80%

t_{ret} = 19,4 min (Method A)

ES-MS [m/z (fragment, intensity)]: 349,0 ($M-H^+$-Fm, 100)

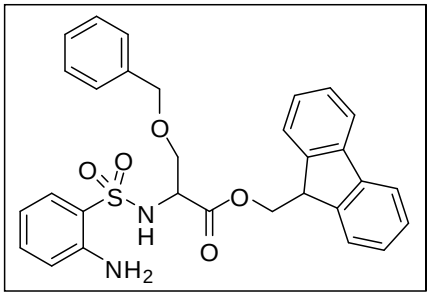
4.6 REDUCTION OF THE NITRO GROUP



4.6.1 GENERAL PROCEDURE

To a suspension of compound **II.101** in 6 ml of a 9/1 mixture of DMF/MeOH, is added chromium(II) chloride (0.433 g, 3.52 mmol, 8 eq) in one portion. This reaction mixture is allowed to shake for 1 h, followed by filtrating and washing the resin 3x with DMF, MeOH and CH_2Cl_2. This procedure is repeated for a second time, delivering the desired aniline **II.102**.

This reaction was optimized for compound **II.102**, with R_1 = Bn and R_2 = H. LC-MS analysis after cleavage from the solid support delivered the following result:



Formula: $C_{30}H_{28}N_2O_5S$

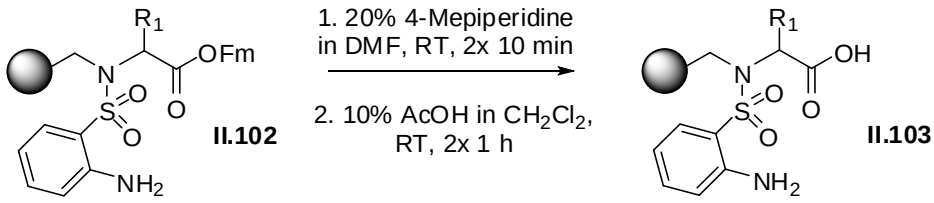
Molecular weight: 528,61 g/mol

LC-MS:

t_{ret} = 19,4 min (Method A)

ES-MS [m/z (fragment, intensity)]: 529,1 ($M+H^+$, 100), 351,0 ($M+H^+$-Fm, 5), 261,0 ($M+H^+$-Fm-Bn, 5)

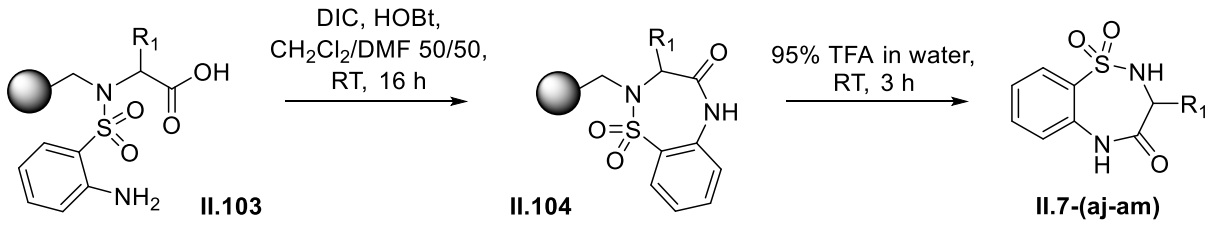
4.7 FLUORENYLMETHYL REMOVAL



4.7.1 GENERAL PROCEDURE

Compound **II.102** is suspended in a 20% solution of 4-methylpiperidine in DMF, shaken for 10 min at room temperature and subsequently filtered off and washed 3 times with DMF, MeOH and CH_2Cl_2. This procedure is repeated for a second time, followed by the removal of residual 4-methylpiperidine by shaking the resin 2x in the presence of a 10% acetic acid solution in CH_2Cl_2. This readily delivered ring closing precursor **III.103**.

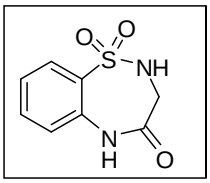
4.8 RING CLOSURE AND CLEAVAGE FROM THE SOLID SUPPORT



4.8.1 GENERAL PROCEDURE

To a suspension of ring closing precursor **II.103** (0.44 mmol, 1 eq) in a 50/50 mixture of CH_2Cl_2/DMF is added HOBt (0.178 g, 1.32 mmol, 3 eq) and DIC (0.204 ml, 1.32 mmol, 3 eq). This reaction mixture is stirred for 16 h at room temperature, filtered off and washed consecutively 3x with DMF, MeOH and CH_2Cl_2. Subsequently, the ring closed benzothiadiazepinone **II.104** is cleaved from the solid support by treating the resin 3 h with a 95% solution of TFA in water, followed by filtration and washing the solid support with CH_2Cl_2. After evaporating the solvents under reduced pressure, the crude product is purified by column chromatography, yielding the desired final products **II.7-(aj-am)**.

4.8.2 2,3-DIHYDRO-1,2,5-BENZOTHIADIAZEPIN-4(5*H*)-ONE-1,1-DIOXIDE **II.7-AJ**



Formula: $C_8H_8N_2O_3S$ (colorless oil)

Molecular weight: 212,23 g/mol

Yield: < 1%

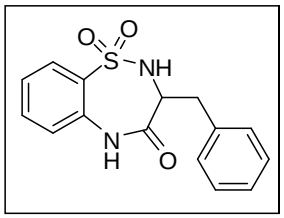
LC-MS:

t_{ret} = 11,8 min (Method A)

ES-MS [m/z (fragment, intensity)]: 211,0 ($M\text{-}H^+$, 100)

TLC: R_f = 0,14 (hexane/EtOAc 60/40)

4.8.3 3-BENZYL-2,3-DIHYDRO-1,2,5-BENZOTHIADIAZEPIN-4(5*H*)-ONE-1,1-DIOXIDE **II.7-AK**



Formula: $C_{15}H_{14}N_2O_3S$ (white solid)

Molecular weight: 302,35 g/mol

Yield: 4%

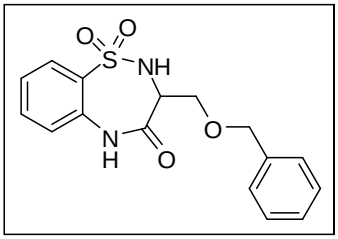
LC-MS:

t_{ret} = 14,3 min (Method A)

ES-MS [m/z (fragment, intensity)]: 301,0 ($M\text{-}H^+$, 100)

TLC: R_f = 0,17 (hexane/EtOAc 60/40)

4.8.4 3-(BENZYLOXYMETHYL)-2,3-DIHYDRO-1,2,5-BENZOTHIADIAZEPIN-4(5*H*)-ONE-1,1-DIOXIDE **II.7-AL**



Formula: $C_{16}H_{16}N_2O_4S$ (white solid)

Molecular weight: 332,37 g/mol

Yield: 6%

LC-MS:

t_{ret} = 14,7 min

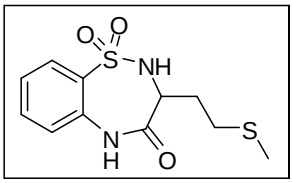
ES-MS [m/z (fragment, intensity)]: 331,0 ($M\text{-}H^+$, 100)

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 8.53 - 8.67 (m, 1 H) 7.94 (dd, *J*=7.9, 1.1 Hz, 1 H) 7.46 - 7.57 (m, 1 H) 7.29 - 7.38 (m, 3 H) 7.19 - 7.26 (m, 3 H) 7.06 (d, *J*=7.9 Hz, 1 H) 5.48 (d, *J*=7.5 Hz, 1 H) 4.48 - 4.59 (m, 2 H) 4.37 - 4.45 (m, 1 H) 4.18 (dd, *J*=9.4, 4.0 Hz, 1 H) 3.86 (dd, *J*=9.2, 3.4 Hz, 1 H)

^{13}C NMR: (75 MHz, CHLOROFORM-*d*) δ 171.36 (C=O) 136.82 (C) 134.06 (C) 133.91 (CH) 131.75 (C) 128.56 (CH) 128.17 (CH) 127.88 (CH) 127.48 (CH) 124.08 (CH) 121.56 (CH) 73.68 (CH_2) 69.48 (CH_2) 57.24 (CH) ppm

TLC: R_f = 0,07 (hexane/EtOAc 70/30)

4.8.5 2,3-DIHYDRO-3-(2-(METHYLTHIO)ETHYL)-1,2,5-BENZOTHIADIAZEPIN-4(5*H*)-ONE-1,1-DIOXIDE **II.7-AM**



Formula: $C_{11}H_{14}N_2O_3S_2$ (white solid)

Molecular weight: 286,37 g/mol

Yield: <1%

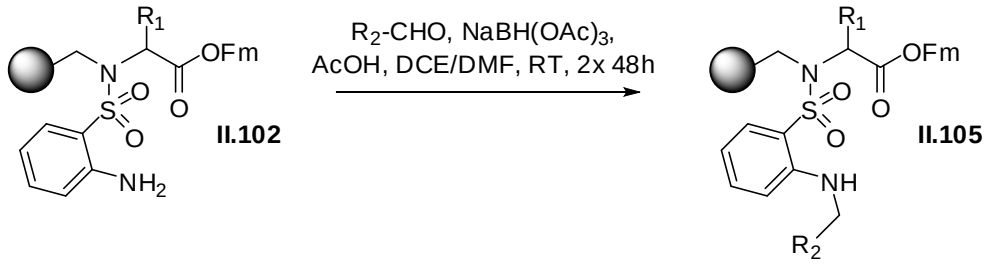
LC-MS:

t_{ret} = 13,1 min

ES-MS [m/z (fragment, intensity)]: 285,0 ($M\text{-}H^+$, 100)

TLC: R_f = 0,07 (hexane/EtOAc 70/30)

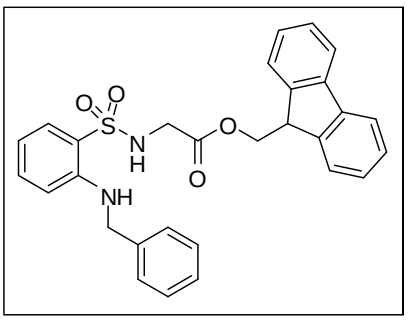
4.9 N_5 ALKYLATION



4.9.1 GENERAL PROCEDURE

To a suspension of aniline **II.102** (0.065 mmol, 1 eq) in a 9/1 mixture of DCE/DMF is added consecutively the aldehyde (0.650 mmol, 10 eq), acetic acid (0.039 ml, 0.650 mmol, 10 eq) and $NaBH(OAc)_3$ (0.055g, 0.262 mmol, 4 eq). This reaction is allowed to stir for 48 h at room temperature before the resin is filtered off again and washed 3x with DMF, MeOH and CH_2Cl_2. This whole procedure is repeated for a second time, yielding the alkylated compound **II.105**.

This reaction was optimized for compound **II.105**, with R_1 = H and R_2 = Ph. LC-MS analysis after cleavage delivered the following result:



Formula: $C_{29}H_{26}N_2O_4S$

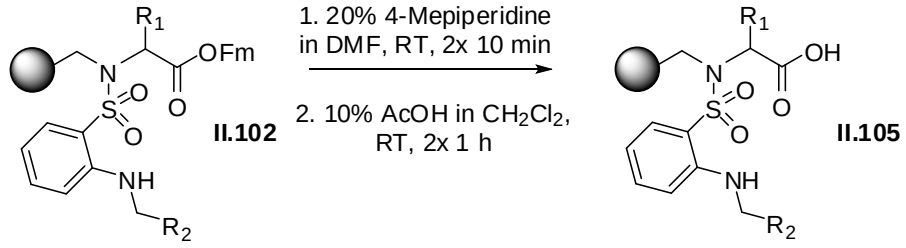
Molecular weight: 498,59 g/mol

LC-MS:

t_{ret} = 19,7 min (Method A)

ES-MS [m/z (fragment, intensity)]: 319,0 ($M\text{-}H^+$-Fm, 100)

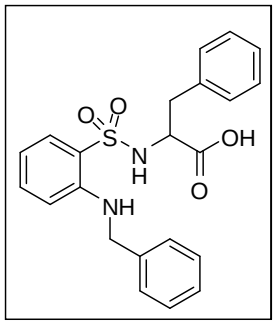
4.10 FLUORENYLMETHYL REMOVAL



4.10.1 GENERAL PROCEDURE

see section 4**.7**

This reaction was optimized for compound **II.105**, with R_1 = Bn and R_2 = Ph. LC-MS analysis after cleavage delivered the following result:



Formula: $C_{22}H_{22}N_2O_4S$

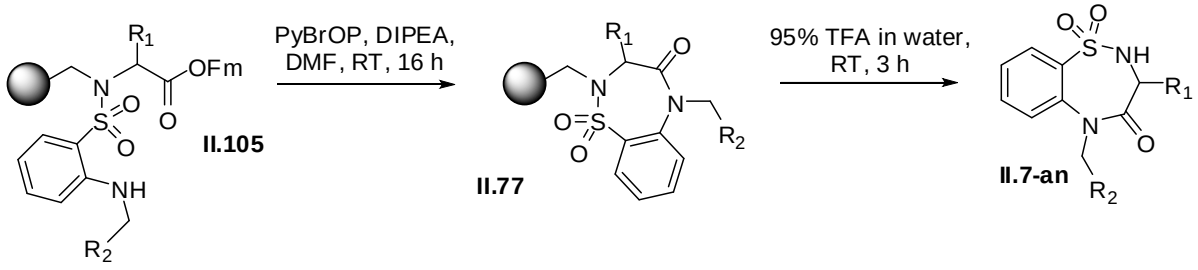
Molecular weight: 410,49 g/mol

LC-MS:

t_{ret} = 5,0 min (Method C)

ES-MS [m/z (fragment, intensity)]: 409,1 ($M\text{-}H^+$, 20), 819,1 ($2M\text{-}H^+$, 2,5)

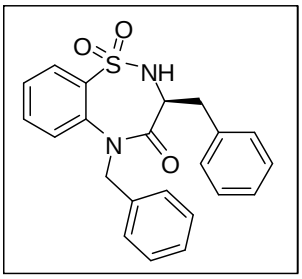
4.11 RING CLOSURE AND CLEAVAGE FROM THE SOLID SUPPORT



4.11.1 GENERAL PROCEDURE

The resin **II.105** (10 mg, 0.0062 mmol, 1 eq) is suspended in 0.3 ml DMF, followed by the consecutive addition of DIPEA (11µl, 0.062 mmol, 10 eq) and PyBrOP (14 mg, 0.031 mmol, 5 eq). This suspension is shaken for 16 h at room temperature, then filtrated and washed 3x with DMF, MeOH and CH_2Cl_2. The ring closed product **II.7** is subsequently cleaved from the solid support by shaking the resin for 3 h in a 95% solution of TFA in water at room temperature. The resin was then filtered off, the filtrate collected in a flask and evaporated under reduced pressure, readily delivering the N_5 alkylated benzothiadiazepinone **II.7-an**.

4.11.2 (3S)-3,5-DIBENZYL-2,3-DIHYDRO-1,2,5-BENZOTHIADIAZEPIN-4(5*H*)-ONE-1,1-DIOXIDE **II.7-AN**



Formula: $C_{22}H_{20}N_2O_3S$ (white solid)

Molecular weight: 392,47 g/mol

Yield: 4%

LC-MS:
t_{ret} = 6,4 min (Method C)
ES-MS [m/z (fragment, intensity)]: 391,1 ($M-H^+$, 100)

HR-MS (ESI): calculated for [$M-H^+$] = 391,1122, found 391,1135

^{1}H NMR: (300 MHz, CHLOROFORM-*d*) δ ppm 7.87 (dd, *J*=7.8, 1.6 Hz, 1 H) 7.55 (td, *J*=7.7, 1.5 Hz, 1 H) 7.42 (td, *J*=7.7, 1.1 Hz, 1 H) 7.28 - 7.36 (m, 6 H) 7.16 - 7.26 (m, 5 H) 5.56 (d, *J*=15.6 Hz, 1 H) 4.69 (d, *J*=3.0 Hz, 1 H) 4.49 (d, *J*=15.4 Hz, 1 H) 3.62 - 3.73 (m, 1 H) 3.22 - 3.30 (m, 1 H) 3.12 - 3.22 (m, 1 H)

^{13}C NMR: (75 MHz, CHLOROFORM-*d*) δ 166.95 (C=O) 140.47 (C) 136.76 (C) 135.51 (C) 134.18 (CH) 129.64 (CH) 129.06 (CH) 128.73 (CH) 127.77 (CH) 127.63 (CH) 127.51 (CH) 127.49 (CH) 126.78 (CH) 124.86 (CH) 56.96 (CH) 53.86 (CH_2) 37.58 (CH_2)

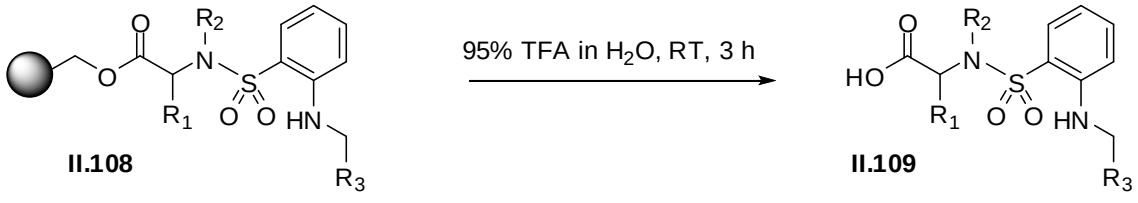
TLC: R_f = 0,07 (hexane/EtOAc 80/20)

Chiral LC:

Column & eluent: Chiralpak IB, 30 min isocratic n-hexane/Ethanol 70/30
Enantiomeric ratio: (3S)/(3R) 97,5/2,5

5 RING CLOSURE OF 2,3-DIHYDRO-1,2,5-BENZOTHIADIAZEPIN-4(5*H*)-ONE-1,1-DIOXIDES IN SOLUTION

5.1 CLEAVAGE FROM THE SOLID SUPPORT

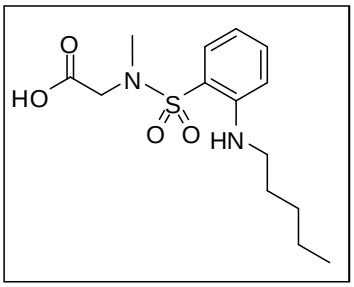


II.108 **II.109**

5.1.1 GENERAL PROCEDURE

Ring closing precursor **II.108** is suspended in a solution of 95% TFA in water and shaken for 3 h at room temperature. Subsequently, the resin is filtered off and washed with CH_2Cl_2 and the filtrate is collected and evaporated under reduced pressure. This crude product is then purified using column chromatography, readily delivering carboxylic acid **II.109**

5.1.2 2-(N-METHYL-N-(2-PENTYLAMINOPHENYLSULFONYL)AMINO ACETIC ACID **II.109-A**



Eluent: hexane/ethyl acetate/acetic acid 80/20/1

Yield: 50% (colorless oil)

Formula: $C_{14}H_{21}N_2O_4S$

Molecular weight: 314,40 g/mol

LC-MS:

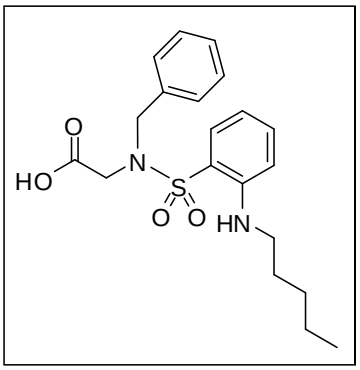
t_{ret} = 12,8 min
ES-MS [m/z (fragment, intensity)]: 313,1 ($M\text{-}H^+$, 100)

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 7.68 (dd, *J*=7.9, 1.5 Hz, 1 H) 7.40 (ddd, *J*=8.5, 7.1, 1.7 Hz, 1 H) 6.65 - 6.79 (m, 2 H) 4.03 (s, 2 H) 3.12 (t, *J*=7.2 Hz, 2 H) 2.88 (s, 3 H) 1.67 (quin, *J*=7.2 Hz, 2 H) 1.22 - 1.49 (m, 5 H) 0.84 - 1.01 (m, 3 H)

^{13}C NMR: (75 MHz, CHLOROFORM-*d*) 173.13 (OC=O), 146.89 (C), 134.89 (CH), 130.66 (CH), 118.38 (C), 115.62 (CH), 112.49 (CH), 50.65 (CH_2), 43.32 (CH_2), 35.87 (CH_3), 29.25 (CH_2), 28.60 (CH_2), 22.38 (CH_2), 13.97 (CH_3) ppm

TLC: R_f = 0,17 (hexane/EtOAc/AcOH 60/40/1)

5.1.3 2-(N-BENZYL-N-(2-PENTYLAMINOPHENYLSULFONYL)AMINO ACETIC ACID **II.109-B**



Eluent: hexane/ethyl acetate/acetic acid 80/20/1

Yield: 32% (colorless oil)

Formula: $C_{20}H_{26}ClN_2O_4S$

Molecular weight: 390,50 g/mol

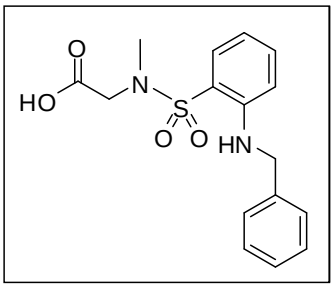
LC-MS:
t_{ret} = 14,3 min
ES-MS [m/z (fragment, intensity)]: 389,1 ($M\text{-}H^+$, 100)

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 7.77 (dd, *J*=7.9, 1.5 Hz, 1 H) 7.40 (ddd, *J*=8.5, 7.1, 1.5 Hz, 1 H) 7.27 - 7.33 (m, 3 H) 7.11 - 7.21 (m, 2 H) 6.66 - 6.79 (m, 2 H) 4.44 (s, 2 H) 3.93 (s, 2 H) 3.13 (t, *J*=7.2 Hz, 2 H) 1.65 (quin, *J*=7.5 Hz, 2 H) 1.23 - 1.45 (m, 5 H) 0.81 - 0.98 (m, 3 H)

^{13}C NMR: (75 MHz, CHLOROFORM-*d*) 173.29 (OC=O), 146.80 (C), 135.01 (CH), 134.67 (C), 130.86 (CH), 128.78 (CH), 128.62 (CH), 128.24 (CH), 119.33 (C), 115.69 (CH), 112.41 (CH), 51.62 (CH_2), 46.51 (CH_2) 43.33 (CH_2), 29.27 (CH_2), 28.63 (CH_2), 22.39 (CH_2), 13.97 (CH_3) ppm

TLC: R_f = 0,09 (hexane/EtOAc/acetic acid 60/40/1)

5.1.4 2-N-METHYL-N-(2-BENZYLAMINOPHENYLSULFONYL)AMINO ACETIC ACID **II.109-C**



Eluent: hexane/ethyl acetate/acetic acid 80/20/1

Yield: 49% (colorless oil)

Formula: $C_{16}H_{18}N_2O_4S$

Molecular weight: 334,39 g/mol

LC-MS:

t_{ret} = 12,1 min

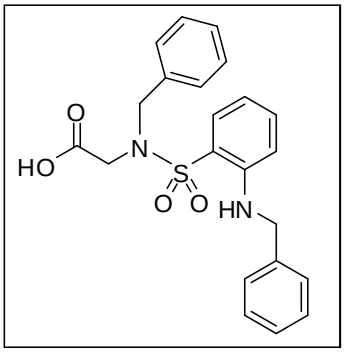
ES-MS [m/z (fragment, intensity)]: 333,1 ($M\text{-}H^+$, 100)

^{1}H NMR (300 MHz, Acetone- d_6) δ ppm 7.68 (dd, *J*=8.1, 1.5 Hz, 1 H) 7.39 - 7.48 (m, 2 H) 7.34 (t, *J*=7.3 Hz, 3 H) 7.20 - 7.29 (m, 1 H) 6.95 (br. s., 1 H) 6.76 (d, *J*=8.5 Hz, 1 H) 6.70 (t, *J*=7.6 Hz, 1 H) 4.51 (br. s., 2 H) 4.07 (s, 2 H) 2.88 (s, 3 H)

^{13}C NMR: (75 MHz, Acetone-d_6) 170.54 (OC=O), 147.47 (C), 140.15 (C), 135.35 (CH), 131.41 (CH), 129.52 (CH), 128.05 (CH), 127.96 (CH), 120.32 (C), 116.32 (CH), 113.81 (CH), 50.92 (CH_2), 47.50 (CH_2), 36.25 (CH_3) ppm

TLC: R_f = 0,13 (hexane/EtOAc/acetic acid 60/40/1)

5.1.5 2-N-BENZYL-N-(2-BENZYLAMINOPHENYLSULFONYL)AMINO ACETIC ACID **II.109-D**



Eluent: hexane/ethyl acetate/acetic acid 80/20/1

Yield: 51% (colorless oil)

Formula: $C_{22}H_{22}N_2O_4S$

Molecular weight: 410,49

LC-MS:

t_{ret} = 13,7 min

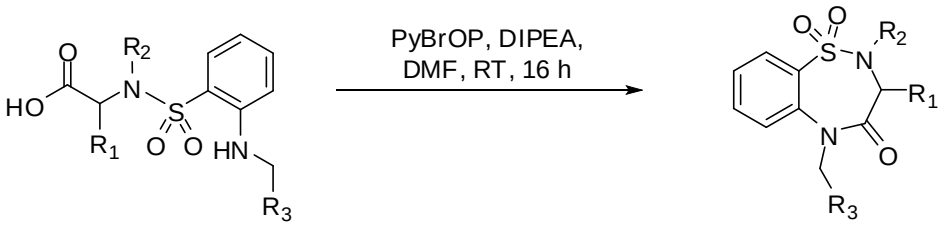
ES-MS [m/z (fragment, intensity)]: 409,1 ($M\text{-}H^+$, 100)

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 7.78 (dd, *J*=7.9, 1.5 Hz, 1 H) 7.28 - 7.35 (m, 2 H) 7.17 - 7.25 (m, 3 H) 7.05 - 7.16 (m, 2 H) 6.63 - 6.76 (m, 2 H) 4.43 (s, 2 H) 4.37 (s, 2 H) 3.91 (s, 2 H)

^{13}C NMR: (75 MHz, CHLOROFORM-*d*) 174.16 (OC=O), 146.46 (C), 138.09 (C), 134.97 (CH), 134.64 (C), 130.81 (CH), 128.81 (CH), 128.75 (CH), 128.61 (CH), 128,24 (CH), 127.35 (CH), 127.02 (CH), 119.76 (C), 112,12 (CH) 112,84 (CH) 51.64 (CH_2), 47.38 (CH_2) 46.40 (CH_2) ppm

TLC: R_f = 0,23 (hexane/EtOAc/AcOH 60/40/1)

5.2 RING CLOSURE IN SOLUTION

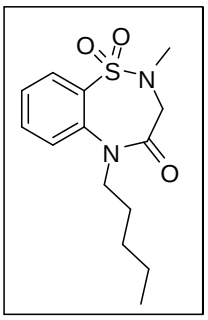


II.109-(ao-ar) **II.7-(ao-ar)**

5.2.1 GENERAL PROCEDURE

The carboxylic acid (0.102 mmol, 1 eq) is brought in a dried flask and dissolved in 1 ml of dry DMF. Subsequently, dry DIPEA (0.177 ml, 1.02 mmol, 10 eq) and PyBrOP (0.238 g, 0.510 mmol, 10 eq) are added to this mixture and this reaction mixture is continued to stir for 4 h at room temperature. The resulting brown reaction mixture is then quenched with 10 ml of a 1 M HCl solution and brought into a seperating funnel. The aqueous layer is then extracted 3x with 5 ml of EtOAc, the collected organic phases are washed with 10 ml brine, dried on $MgSO_4$, and evaporated under reduced pressure. The resulting brownish oil is purified using column chromatography, delivering the desired N_5 alkylated 2,3-dihydro-1,2,5-benzothiadiazepin-4(5*H*)-one-1,1-dioxides **II.7-(ao-ar)**.

5.2.2 2,3-DIHYDRO-2-METHYL-5-PENTYL-1,2,5-BENZOTHIADIAZEPIN-4(5*H*)-ONE-1,1-DIOXIDE **II.7-AO**



Formula: $C_{14}H_{20}N_2O_3S$ (white solid)

Molecular weight: 296,39 g/mol

Yield: 30%

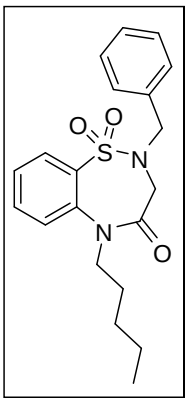
LC-MS:
t_{ret} = 16,5 min
ES-MS [m/z (fragment, intensity)]: 297,1 ($M+H^+$, 95), 226,1 ($M+H^+$-pentyl, 5)

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 7.91 (dd, *J*=8.5, 1.7 Hz, 1 H) 7.66 - 7.74 (m, 1 H) 7.40 - 7.49 (m, 2 H) 3.76 - 3.89 (m, 2 H) 3.36 (br. s., 2 H) 2.72 (s, 3 H) 1.59 - 1.74 (m, 2 H) 1.19 - 1.35 (m, 4 H) 0.85 (t, *J*=6.6 Hz, 3 H)

^{13}C NMR: (75 MHz, CHLOROFORM-*d*) δ 165.21 (C=O) 141.08 (C) 134.33 (CH) 128.90 (C) 128.17 (C) 126.70 (CH) 124.38 (CH) 55.89 (CH_2) 49.80 (CH_2) 38.25 (CH_3) 29.21 (CH_2) 27.16 (CH_2) 22.26 (CH_2) 13.96 (CH_3) ppm

TLC: R_f = 0,05 (hexane/ether 70/30)

5.2.3 2-BENZYL-2,3-DIHYDRO-5-PENTYL-1,2,5-BENZOTHIADIAZEPIN-4(5*H*)-ONE-1,1-DIOXIDE **II.7-AP**



Formula: $C_{20}H_{24}N_2O_3S$ (white solid)

Molecular weight: 372,48 g/mol

Yield: 24%

LC-MS:
t_{ret} = 6,9 min (method C)
ES-MS [m/z (fragment, intensity)]: 371,1 ($M\text{-}H^+$, 100)

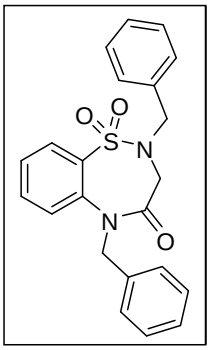
HR-MS (ESI): calculated for [$M\text{-}H^+$] = 371,1435, found 371,1442

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 7.97 (d, *J*=7.9 Hz, 1 H) 7.68 (td, *J*=7.9, 1.5 Hz, 1 H) 7.38 - 7.48 (m, 2 H) 7.27 - 7.34 (m, 5 H) 4.29 (s, 2 H) 3.75 - 3.88 (m, 2 H) 3.22 (s, 2 H) 1.55 - 1.72 (m, 3 H) 1.16 - 1.35 (m, 4 H) 0.85 (t, *J*=6.8 Hz, 3 H)

^{13}C NMR: (75 MHz, CHLOROFORM-*d*) δ 165.57 (C=O) 141.05 (C) 134.24 (CH) 134.06 (C) 130.27 (C) 128.81 (CH) 128.75 (CH) 128.25 (CH) 127.81 (CH) 126.63 (CH) 124.23 (CH) 54.43 (CH_2) 52.42 (CH_2) 49.74 (CH_2) 29.19 (CH_2) 27.11 (CH_2) 22.25 (CH_2) 13.94 (CH_3) ppm

TLC: R_f = 0,08 (hexane/ether 70/30)

5.2.4 2,5-DIBENZYL-2,3-DIHYDRO-1,2,5-BENZOTHIADIAZEPIN-4(5*H*)-ONE-1,1-DIOXIDE **II.7-AQ**



Formula: $C_{22}H_{20}N_2O_3S$ (white solid)

Molecular weight: 392,47 g/mol

Yield: 35%

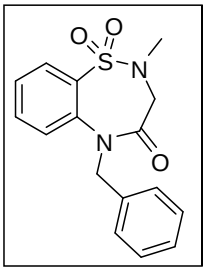
LC-MS:
t_{ret} = 6,6 min (method C)
ES-MS [m/z (fragment, intensity)]: 391,1 ($M\text{-}H^+$, 100)

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 7.95 (dd, *J*=7.8, 1.6 Hz, 3 H) 7.53 (td, *J*=7.5, 1.7 Hz, 3 H) 7.40 (td, *J*=7.7, 1.1 Hz, 3 H) 7.27 - 7.34 (m, 30 H) 7.17 - 7.24 (m, 4 H) 5.02 (s, 6 H) 4.32 (s, 6 H) 3.36 (s, 6 H)

^{13}C NMR: (75 MHz, CHLOROFORM-*d*) δ 166.20 (C=O) 141.20 (C) 136.74 (C) 134.12 (CH) 133.92 (C) 129.74 (C) 128.89 (CH) 128.79 (CH) 128.69 (CH) 128.34 (CH) 127.76 (CH) 127.67 (CH) 127.61 (CH) 126.92 (CH) 124.22 (CH) 54.56 (CH_2) 53.12 (CH_2) 52.40 (CH_2) ppm

TLC: R_f = 0,10 (hexane/ether 70/30)

5.2.5 5-BENZYL-2,3-DIHYDRO-2-METHYL-1,2,5-BENZOTHIADIAZEPIN-4(5*H*)-ONE-1,1-DIOXIDE **II.7-AR**



Formula: $C_{16}H_{16}N_2O_3S$ (white solid)

Molecular weight: 316,32 g/mol

Yield: 33%

LC-MS:
t_{ret} = 15,8 min
ES-MS [m/z (fragment, intensity)]: 317,0 ($M+H^+$, 100)

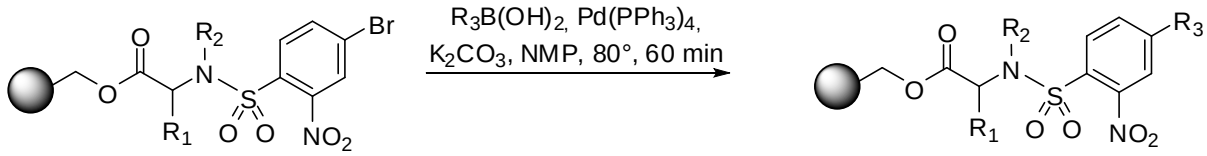
^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 7.90 (dd, *J*=7.8, 1.6 Hz, 1 H) 7.56 (td, *J*=7.8, 1.5 Hz, 1 H) 7.41 (td, *J*=7.6, 1.1 Hz, 1 H) 7.28 - 7.35 (m, 5 H) 7.23 (d, *J*=0.9 Hz, 1 H) 5.02 (s, 2 H) 3.47 (s, 2 H) 2.75 (s, 3 H)

^{13}C NMR: (75 MHz, CHLOROFORM-*d*) δ 165.83 (C=O) 134.20 (C) 128.73 (C) 128.04 (CH) 127.80 (C) 129.64 (C) 126.99 (CH) 124.41 (CH) 55.86 (CH_2) 53.17 (CH_2) 38.31 (CH_3) ppm

TLC: R_f = 0,25 (hexane/ethyl acetate/AcOH 60/40/1)

6 ON-RESIN SUZUKI CROSS COUPLING REACTION

6.1 SYNTHESIS OF 7-ARYL-2,3-DIHYDRO-1,2,5-BENZOTHIADIAZEPIN-4(5H)-ONE-1,1-DIOXIDES **II.121**

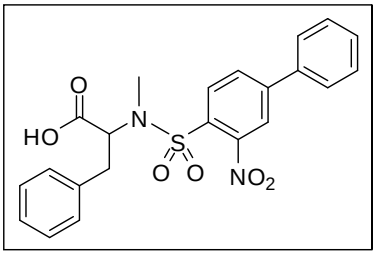


II.119 **II.120**

6.1.1 GENERAL PROCEDURE

To the bromo containing resin **II.119** (0.470 mmol, 1 eq), brought in a microwave tube, is added subsequently 5 ml of NMP, K_2CO_3 (0.130 g, 0.940 mmol, 2 eq), the boronic acid (1.41 mmol, 3 eq) and $Pd(PPh_3)_4$ (0.109 g, 0.940 mmol, 0.2 eq). This suspension is heated to 80°C for 60 min using microwave heating with constant cooling (Powermax method). The resin is filtered off and washed consecutively 3x with DMF, MeOH and CH_2Cl_2, readily yielding the arylated product **II.120**.

This reaction was optimized for compound **II.120**, with R_1 = Bn and R_2 = Ph. LC-MS analysis after cleavage delivered the following result:

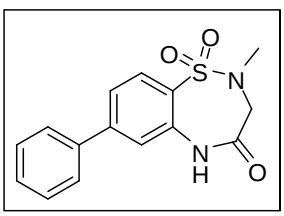


Formula: $C_{22}H_{20}N_2O_6S$

Molecular weight: 440,47 g/mol

LC-MS:
t_{ret} = 13,9 min
ES-MS [m/z (fragment, intensity)]: 439,1 ($M\text{-}H^+$, 80) 879,2 ($2M\text{-}H^+$, 80)

6.1.2 2,3-DIHYDRO-2-METHYL-7-PHENYL-1,2,5-BENZOTHIADIAZEPIN-4(5*H*)-ONE-1,1-DIOXIDE **II.121-A**



Formula: $C_{15}H_{14}N_2O_3S$ (white solid)

Molecular weight: 302,35 g/mol

Yield: 8%

LC-MS:

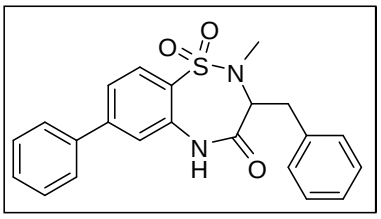
t_{ret} = 15,6 min
ES-MS [m/z (fragment, intensity)]: 301,0 ($M\text{-}H^+$, 100)

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 10.65 (br. s., 1 H) 7.84 (d, *J*=8.3 Hz, 1 H) 7.64 - 7.74 (m, 3 H) 7.45 - 7.59 (m, 4 H) 4.27 (s, 2 H) 2.76 (s, 3 H)

^{13}C NMR: (75 MHz, DMSO-d_6) δ 170.43 (C=O) 145.65 (C) 137.96 (C) 135.19 (C) 129.20 (CH) 128.84 (CH) 126.85 (CH) 126.25 (C) 121.40 (CH) 119.52 (CH) 54.06 (CH_2) 36.09 (CH_3) ppm

TLC: R_f = 0,20 (hexane/EtOAc 60/40)

6.1.3 3-BENZYL-2,3-DIHYDRO-2-METHYL-7-PHENYL-1,2,5-BENZOTHIADIAZEPIN-4(5*H*)-ONE-1,1-DIOXIDE **II.121-B**



Formula: $C_{22}H_{20}N_2O_3S$ (white solid)

Molecular weight: 392,47 g/mol

Yield: 14%

LC-MS:

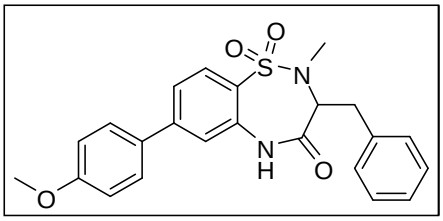
t_{ret} = 17,8 min
ES-MS [m/z (fragment, intensity)]: 391,1 ($M-H^+$, 100)
Purity: 82%

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 10.58 (s, 1 H) 7.79 (d, *J*=8.3 Hz, 1 H) 7.62 - 7.69 (m, 3 H) 7.42 - 7.57 (m, 5 H) 7.18 - 7.37 (m, 4 H) 4.81 (dd, *J*=10.1, 4.8 Hz, 1 H) 3.39 (dd, *J*=14.5, 4.9 Hz, 1 H) 3.03 (dd, *J*=14.5, 10.2 Hz, 1 H) 2.66 (s, 3 H)

^{13}C NMR: (75 MHz, DMSO-d_6) δ 170.90 (C=O) 145.16 (C) 137.98 (C) 137.34 (C) 134.28 (C) 129.37 (CH) 129.20 (CH) 128.92 (CH) 128.79 (CH) 128.10 (CH) 127.62 (CH) 126.82 (CH) 126.31 (CH) 121.66 (CH) 119.69 (CH) 61.43 (CH) 34.78 (CH_2) 32.29 (CH_3) ppm

TLC: R_f = 0,38 (hexane/EtOAc 60/40)

6.1.4 3-BENZYL-2,3-DIHYDRO-2-METHYL-7-(4-METHOXYPHENYL)-1,2,5-BENZOTHIADIAZEPIN-4(5H)-ONE-1,1-DIOXIDE **II.121-C**



Formula: $C_{23}H_{22}N_2O_4S$ (white solid)

Molecular weight: 422,50 g/mol

Yield: 19%

LC-MS:

t_{ret} = 17.7 min
ES-MS [m/z (fragment, intensity)]: 423.1 ($M+H^+$, 35), 395.1 (M-28, 60), 440.1 ($M+NH_4^+$, 5)
Purity: 94%

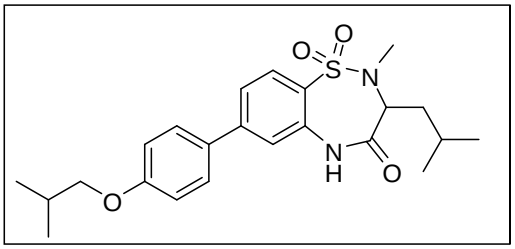
HR-MS (ESI): calculated for [$M+H^+$] = 423,1373, found 423,1377

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 8.39 (s, 1 H) 7.92 (d, *J*=8.1 Hz, 1 H) 7.48 - 7.56 (m, 2 H) 7.39 (dd, *J*=8.3, 1.7 Hz, 1 H) 7.28 - 7.37 (m, 4 H) 7.17 (d, *J*=1.7 Hz, 1 H) 6.95 - 7.03 (m, 2 H) 4.71 (dd, *J*=9.0, 5.5 Hz, 1 H) 3.85 (s, 3 H) 3.64 (dd, *J*=14.6, 5.6 Hz, 1 H) 3.15 (dd, *J*=14.5, 9.0 Hz, 1 H) 2.74 (s, 3 H)

^{13}C NMR: (75 MHz, CHLOROFORM-*d*) δ 171.76 (C=O) 160.43 (C) 146.52 (C) 136.65 (C) 133.12 (C) 130.65 (C) 129.75 (CH) 129.34 (CH) 128.60 (CH) 128.31 (CH) 127.35 (C) 126.89 (CH) 122.49 (CH) 118.94 (CH) 114.61 (CH) 62.36 (CH3) 55.41 (CH) 35.96 (CH_2) 32.72 (CH_3) ppm

TLC: R_f = 0,30 (hexane/EtOAc 60/40)

6.1.5 2,3-DIHYDRO-7-(4-ISOBUTOXYPHENYL)-3-ISOBUTYL-2-METHYL-1,2,5-BENZOTHIADIAZEPIN-4(5*H*)-ONE-1,1-DIOXIDE **II.121-D**



Formula: $C_{23}H_{30}N_2O_4S$ (white solid)

Molecular weight: 430,56 g/mol

Yield: 39%

LC-MS:

t_{ret} = 20,0 min

ES-MS [m/z (fragment, intensity)]: 429.1 ($M-H^+$, 100)

Purity: 100%

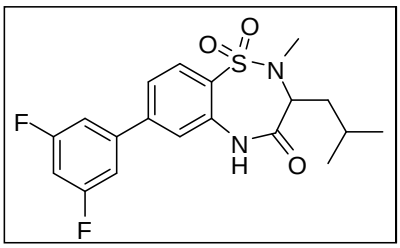
HR-MS (ESI): calculated for [$M-H^+$] = 429,1854, found 429,1851

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 8.35 (s, 1 H) 7.94 - 8.01 (m, 1 H) 7.46 - 7.55 (m, 2 H) 7.42 (dd, *J*=8.4, 1.6 Hz, 1 H) 7.14 (d, *J*=1.5 Hz, 1 H) 6.94 - 7.03 (m, 2 H) 4.67 - 4.78 (m, 1 H) 3.77 (d, *J*=6.6 Hz, 2 H) 2.82 (s, 3 H) 2.12 (spt, *J*=6.8 Hz, 1 H) 1.74 - 1.99 (m, 3 H) 0.95 - 1.11 (m, 12 H)

^{13}C NMR: (75 MHz, CHLOROFORM-*d*) δ 172.81 (C=O) 160.15 (C) 146.48 (C) 132.54 (C) 130.35 (C) 129.99 (CH) 128.22 (CH) 127.19 (C) 122.49 (CH) 118.73 (CH) 115.16 (C) 74.59 (CH_2) 57.28 (CH) 36.75 (CH_2) 30.41 (CH_3) 28.24 (CH) 23.85 (CH_3) 23.37 (CH_3) 21.09 (CH_3) 19.21 (CH_3) ppm

TLC: R_f = 0,52 (hexane/EtOAc 60/40)

6.1.6 7-(3,5-DIFLUOROPHENYL)-2,3-DIHYDRO-3-ISOBUTYL-2-METHYL-1,2,5-BENZOTHIADIAZEPIN-4(5*H*)-ONE-1,1-DIOXIDE **II.121-E**



Formula: $C_{19}H_{20}F_2N_2O_3S$ (white solid)

Molecular weight: 394,44 g/mol

Yield: 5%

LC-MS:

t_{ret} = 18,5 min

ES-MS [m/z (fragment, intensity)]: 393.0 ($M-H^+$, 100)

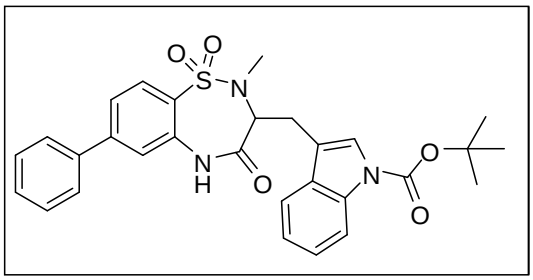
Purity: 97%

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 9.12 (s, 1 H) 8.04 (d, *J*=8.3 Hz, 1 H) 7.42 (dd, *J*=8.3, 1.7 Hz, 1 H) 7.33 (d, *J*=1.7 Hz, 1 H) 7.06 - 7.17 (m, 2 H) 6.83 - 6.95 (m, 1 H) 4.69 - 4.83 (m, 1 H) 2.83 (s, 3 H) 1.76 - 2.05 (m, 3 H) 1.01 (dd, *J*=10.0, 6.2 Hz, 6 H)

^{13}C NMR: (75 MHz, CHLOROFORM-*d*) δ 173.50 (C=O) 165.20 (dd, *J*=249.74, 13.18 Hz, 2xC) 144.11 (C) 141.56 (t, *J*=9.33 Hz, C) 132.95 (C) 130.38 (CH) 129.08 (C) 122.62 (CH) 119.69 (CH) 110.14 (dd, *J*=25.8, 8.24 Hz, CH) 104.22 (t, J=25.25 Hz, CH) 57.47 (CH) 36.74 (CH_2) 30.44 (CH_3) 23.83 (CH_3) 23.23 (CH_3) 20.96 (CH) ppm

TLC: R_f = 0,60 (hexane/EtOAc 60/40)

6.1.7 2-BENZYL-2,3-DIHYDRO-3-ISOBUTYL-7-PHENYL-1,2,5-BENZOTHIADIAZEPIN-4(5*H*)-ONE-1,1-DIOXIDE **II.121-F**



Formula: $C_{29}H_{29}N_3O_5S$ (white solid)

Molecular weight: 531,62 g/mol

Yield: 4%

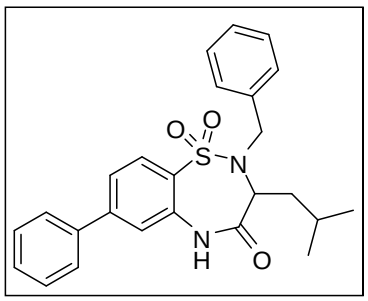
LC-MS:
t_{ret} = 19,8 min
ES-MS [m/z (fragment, intensity)]: 530,1 ($M-H^+$, 100)
Purity: 97%

HR-MS (ESI): calculated for [$M-H^+$] = 530,1755, found 530,1750

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 8.16 (d, *J*=8.1 Hz, 1 H) 8.00 (d, *J*=8.3 Hz, 1 H) 7.71 (s, 1 H) 7.59 - 7.64 (m, 1 H) 7.53 - 7.59 (m, 2 H) 7.40 - 7.52 (m, 4 H) 7.28 - 7.38 (m, 2 H) 7.14 (s, 1 H) 4.88 (dd, *J*=8.5, 5.7 Hz, 1 H) 3.66 - 3.77 (m, 1 H) 3.27 (dd, *J*=15.2, 8.4 Hz, 1 H) 2.83 (s, 3 H) 1.68 (s, 9 H)

TLC: R_f = 0,08 (hexane/EtOAc 80/20)

6.1.8 2-BENZYL-2,3-DIHYDRO-3-ISOBUTYL-7-PHENYL-1,2,5-BENZOTHIADIAZEPIN-4(5*H*)-ONE-1,1-DIOXIDE **II.121-G**



Formula: $C_{25}H_{26}N_2O_3S$ (white solid)

Molecular weight: 434,55 g/mol

Yield: 22%

LC-MS:
t_{ret} = 19,5 min
ES-MS [m/z (fragment, intensity)]: 433,1 ($M-H^+$, 100)
Purity: 92%

HR-MS (ESI): calculated for [$M-H^+$] = 433,1591, found 433,1591

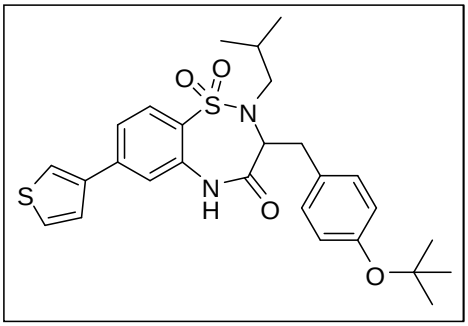
^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 8.24 (br. s., 1 H) 8.05 (d, *J*=8.3 Hz, 1 H) 7.52 - 7.60 (m, 2 H) 7.42 - 7.52 (m, 4 H) 7.34 - 7.42 (m, 2 H) 7.26 - 7.33 (m, 3 H) 7.14 (s, 1 H) 4.58 - 4.74 (m, 2 H) 4.11 (d, *J*=15.8 Hz, 1 H) 1.69 - 1.78 (m, 2 H) 1.56 - 1.68 (m, 1 H) 0.82 (d, *J*=6.4 Hz, 3 H) 0.59 (d, *J*=6.6 Hz, 3 H)

^{13}C NMR: (75 MHz, CHLOROFORM-*d*) δ 173.08 (C=O) 146.79 (C) 138.36 (C) 136.09 (C) 132.74 (C) 129.90 (CH) 129.18 (CH) 128.95 (CH) 128.91 (C) 128.50 (CH) 128.03 (CH) 127.13 (CH) 123.05 (CH) 119.45 (CH) 58.43 (CH) 50.40 (CH_2) 38.20 (CH_2) 23.57 (CH) 22.70 (CH_3) 21.03 (CH_3) ppm

IR (HATR): 3065 (w) 2953 (w) 2358 (w) 2331 (w) 1680 (m) 1605 (w) 1569 (w) 1476 (w) 1400 (m) 1367 (w) 1336 (w) 1226 (w) 1170 (m) 1148 (w) 1090 (w) 1028 (w) 900 (w) 867 (w) 821 (w) 783 (w) 760 (w) 734 (w) 686 (m) 675 (w) 618 (w)

TLC: R_f = 0,62 (hexane/EtOAc 60/40)

6.1.9 3-(4-*TERT*-BUTOXYBENZYL)-2,3-DIHYDRO-2-ISOBUTOXY-7-(3-THIOPHENYL)-1,2,5-BENZOTHIADIAZEPIN-4(5*H*)-ONE-1,1-DIOXIDE
II.121-H



Formula: $C_{27}H_{32}N_2O_4S_2$ (white solid)

Molecular weight: 512,68 g/mol

Yield: 15%

LC-MS:
t_{ret} = 20,0 min
ES-MS [m/z (fragment, intensity)]: 511,1 ($M\text{-}H^+$, 100)

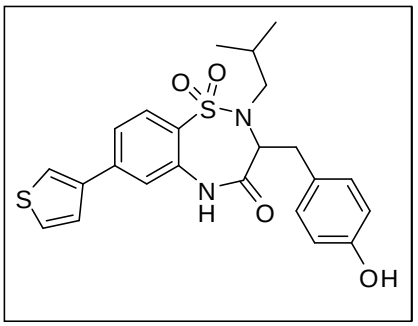
HR-MS (ESI): calculated for [$M\text{-}H^+$] = 511,1731, found 511,1733

^{1}H NMR (300 MHz, Acetone-d_6) δ ppm 9.43 (s, 1 H) 7.91 (dd, *J*=3.0, 1.3 Hz, 1 H) 7.82 (d, *J*=8.1 Hz, 1 H) 7.76 (d, *J*=1.5 Hz, 1 H) 7.64 (dd, *J*=5.1, 3.0 Hz, 1 H) 7.53 - 7.62 (m, 2 H) 7.23 - 7.37 (m, 2 H) 6.89 - 7.02 (m, 2 H) 4.52 (dd, *J*=9.4, 5.1 Hz, 1 H) 3.62 (dd, *J*=14.1, 5.1 Hz, 1 H) 3.32 (dd, *J*=14.1, 9.6 Hz, 1 H) 2.75 - 2.80 (m, 1 H) 2.52 (dd, *J*=14.0, 9.5 Hz, 1 H) 1.39 - 1.57 (m, 1 H) 1.32 (s, 9 H) 0.63 (d, *J*=6.6 Hz, 3 H) 0.58 (d, *J*=6.6 Hz, 3 H)

^{13}C NMR: (75 MHz, Acetone-d_6) δ 172.81 (C=O) 155.25 (C) 141.68 (CH) 140.86 (C) 136.75 (C) 133.92 (C) 131.35 (CH) 129.88 (CH) 129.01 (C) 128.35 (CH) 126.87 (CH) 124.98 (CH) 123.95 (CH) 121.66 (CH) 119.49 (CH) 78.53 (C) 66.96 (CH_2) 58.40 (CH) 39.27 (CH_2) 29.21 (CH_3) 28.03 (CH_3) 20.32 (CH_3) ppm

TLC: R_f = 0,45 (hexane/EtOAc 60/40)

6.1.10 3-(4-HYDROXYBENZYL)-2,3-DIHYDRO-2-ISOBUTOXY-7-(3-THIOPHENYL)-1,2,5-BENZOTHIADIAZEPIN-4(5*H*)-ONE-1,1-DIOXIDE **II.121-I**



Formula: $C_{23}H_{24}N_2O_4S_2$ (white solid)

Molecular weight: 456,58 g/mol

Yield: 11%

LC-MS:
t_{ret} = 17,1 min
ES-MS [m/z (fragment, intensity)]: 455,1 ($M\text{-}H^+$, 100)

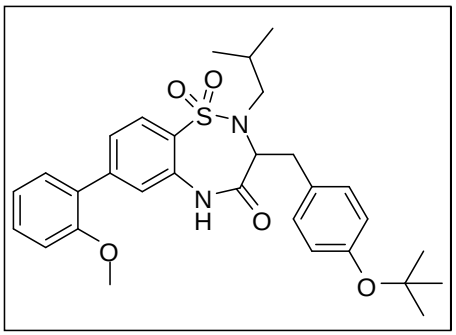
HR-MS (ESI): calculated for [$M\text{-}H^+$] = 455,1105, found 455,1111

^{1}H NMR (300 MHz, Acetone) δ ppm 9.39 (s, 1 H) 7.90 (dd, *J*=3.0, 1.3 Hz, 1 H) 7.82 (d, *J*=8.1 Hz, 1 H) 7.75 (s, 1 H) 7.64 (dd, *J*=5.1, 3.0 Hz, 1 H) 7.53 - 7.62 (m, 2 H) 7.21 (d, *J*=8.3 Hz, 2 H) 6.72 - 6.83 (m, 2 H) 4.48 (ddd, *J*=9.0, 5.5, 1.1 Hz, 1 H) 3.54 (dd, *J*=14.2, 5.4 Hz, 1 H) 3.22 (dd, *J*=14.2, 8.9 Hz, 1 H) 2.86 (dd, *J*=14.0, 5.4 Hz, 1 H) 2.55 (dd, *J*=14.1, 9.4 Hz, 1 H) 1.50 - 1.65 (m, 1 H) 0.68 (d, *J*=6.8 Hz, 3 H) 0.62 (d, *J*=6.4 Hz, 3 H)

^{13}C NMR: (75 MHz, CHLOROFORM-*d*) δ 165.21 (C=O) 141.08 (C) 134.33 (CH) 128.90 (C) 128.17 (C) 126.70 (CH) 124.38 (CH) 55.89 (CH_2) 52.42 (CH_2) 49.80 (CH_2) 29.21 (CH_2) 27.16 (CH_2) 22.26 (CH_2) 13.96 (CH_3) ppm

TLC: R_f = 0,17 (hexane/EtOAc 60/40)

6.1.11 3-(4-*TERT*-BUTOXYBENZYL)-2,3-DIHYDRO-2-ISOBUTOXY-7-(2-METHOXYPHENYL)-1,2,5-BENZOTHIADIAZEPIN-4(5*H*)-ONE-1,1-DIOXIDE **II.121-J**



Formula: $C_{30}H_{36}N_2O_5S$ (white solid)

Molecular weight: 536,68 g/mol

Yield: 21%

LC-MS:
t_{ret} = 19,9 min
ES-MS [m/z (fragment, intensity)]: 535,2 ($M\text{-}H^+$, 100)

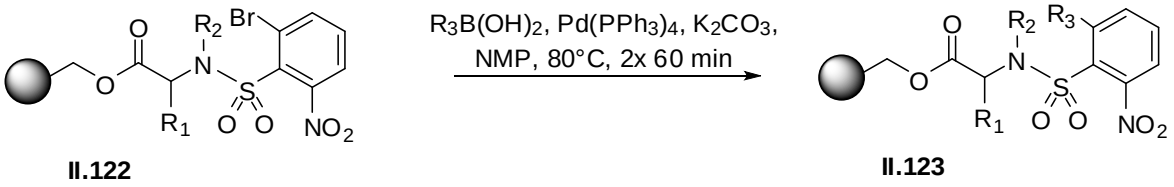
HR-MS (ESI): calculated for [$M\text{-}H^+$] = 535,2272, found 535,2277

^{1}H NMR (300 MHz, Acetone- d_6) δ ppm 9.45 (s, 1 H) 7.82 (d, *J*=8.3 Hz, 1 H) 7.61 (s, 1 H) 7.35 - 7.46 (m, 3 H) 7.26 - 7.35 (m, 2 H) 7.15 (d, *J*=7.7 Hz, 1 H) 7.06 (td, *J*=7.5, 1.0 Hz, 1 H) 6.91 - 7.00 (m, 2 H) 4.54 (dd, *J*=9.8, 4.9 Hz, 1 H) 3.85 (s, 3 H) 3.60 (dd, *J*=14.3, 5.3 Hz, 1 H) 3.31 (dd, *J*=14.1, 9.4 Hz, 1 H) 2.85 (dd, *J*=14.0, 5.2 Hz, 1 H) 2.57 (dd, *J*=14.0, 9.5 Hz, 1 H) 1.42 - 1.63 (m, 1 H) 1.32 (s, 9 H) 0.67 (d, *J*=6.8 Hz, 3 H) 0.61 (d, *J*=6.4 Hz, 3 H)

^{13}C NMR: (125 MHz, Acetone-*d_6*) δ 173.17 (C=O) 158.05 (C) 155.67 (C) 145.67 (C) 136.14 (C) 134.34 (C) 131.81 (CH) 131.76 (CH) 131.46 (CH) 129.44 (C) 129.21 (CH) 125.61 (CH) 125.39 (CH) 123.41 (CH) 123.33 (CH) 122.32 (CH) 113.14 (CH) 78.96 (C) 67.08 (CH) 58.59 (CH_2) 56.49 (CH_3) 39.51 (CH_2) 29.65 (CH) 28.59 (CH_3) 20.78 (CH_3) ppm

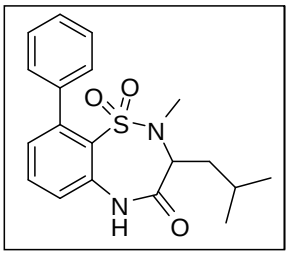
TLC: R_f = 0,41 (hexane/EtOAc 60/40)

6.2 SYNTHESIS OF 9-ARYL-2,3-DIHYDRO-1,2,5-BENZOTHIADIAZEPIN-4(5*H*)-ONE-1,1-DIOXIDES **II.124**



II.122 **II.123**

6.2.1 2,3-DIHYDRO-3-ISOBUTYL-2-METHYL-9-PHENYL-1,2,5-BENZOTHIADIAZEPIN-4(5*H*)-ONE-1,1-DIOXIDE **II.124-A**



Formula: $C_{19}H_{22}N_2O_3S$ (white solid)

Molecular weight: 358,45 g/mol

Yield: 20%

LC-MS:

t_{ret} = 17,6 min

ES-MS [m/z (fragment, intensity)]: 357,1 ($M-H^+$, 100)

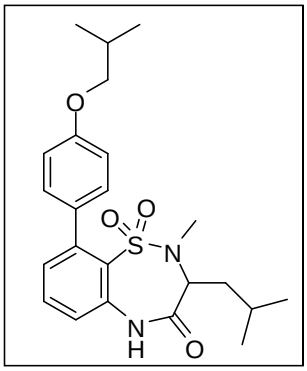
HR-MS (ESI): calculated for [$M-H^+$] = 357,1278, found 357,1280

^{1}H NMR (300 MHz, Acetone-*d_6*) δ ppm 9.26 (br. s., 1 H) 7.56 (t, *J*=8.1 Hz, 1 H) 7.32 - 7.47 (m, 6 H) 7.01 (d, *J*=7.3 Hz, 1 H) 4.71 - 4.80 (m, 1 H) 2.76 (s, 3 H) 1.69 - 1.81 (m, 3 H) 0.97 (t, *J*=6.6 Hz, 6 H)

^{13}C NMR: (75 MHz, Acetone-*d_6*) δ 173.07 (C=O) 145.48 (C) 141.51 (C) 134.67 (C) 132.88 (CH) 130.90 (CH) 128.72 (CH) 128.25 (CH) 128.00 (CH) 122.66 (CH) 56.69 (CH) 37.16 (CH_2) 24.67 (CH) 23.76 (CH_3) 21.56 (CH_3) ppm

TLC: R_f = 0,09 (hexane/EtOAc 80/20)

6.2.2 2,3-DIHYDRO-9-(4-ISOBUTOXYPHENYL)-3-ISOBUTYL-2-METHYL-1,2,5-BENZOTHIADIAZEPIN-4(5*H*)-ONE-1,1-DIOXIDE **II.124-B**



Formula: $C_{23}H_{30}N_2O_4S$ (white solid)

Molecular weight: 430,56 g/mol

Yield: 21%

LC-MS:
t_{ret} = 19,6 min
ES-MS [m/z (fragment, intensity)]: 429,1 ($M\text{-}H^+$, 100)

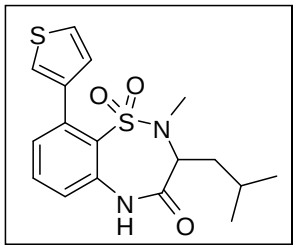
HR-MS (ESI): calculated for [$M\text{-}H^+$] = 429,1854, found 429,1863

^{1}H NMR (300 MHz, Acetone) δ ppm 9.23 (s, 1 H) 7.53 (dd, *J*=8.3, 7.5 Hz, 1 H) 7.39 (d, *J*=8.5 Hz, 1 H) 7.23 - 7.36 (m, 2 H) 7.00 (dd, *J*=7.3, 1.3 Hz, 1 H) 6.85 - 6.96 (m, 2 H) 4.69 - 4.80 (m, 1 H) 3.81 (d, *J*=6.4 Hz, 2 H) 2.70 - 2.78 (m, 3 H) 1.66 - 1.86 (m, 3 H) 1.04 (d, *J*=6.8 Hz, 6 H) 0.92 - 1.01 (m, 6 H)

^{13}C NMR: (75 MHz, Acetone-d_6) δ 173.06 (C=O) 159.77 (C) 145.47 (C) 134.64 (C) 133.53 (C) 132.80 (CH) 132.07 (CH) 129.02 (CH) 122.40 (CH) 122.30 (CH) 114.00 (CH) 74.94 (CH_2) 56.61 (CH) 37.14 (CH_2) 30.02 (CH_3) 29.16 (CH) 24.67 (CH) 23.77 (CH_3) 21.56 (CH_3) 19.57 (CH_3) ppm

TLC: R_f = 0,12 (hexane/EtOAc 80/20)

6.2.3 2,3-DIHYDRO-3-ISOBUTYL-2-METHYL-9-(3-THIOPHENYL)-1,2,5-BENZOTHIADIAZEPIN-4(5*H*)-ONE-1,1-DIOXIDE **II.124-C**



Formula: $C_{17}H_{20}N_2O_3S_2$ (white solid)

Molecular weight: 364,48 g/mol

Yield: 22%

LC-MS:
t_{ret} = 17,4 min
ES-MS [m/z (fragment, intensity)]: 363,0 ($M\text{-}H^+$, 100)

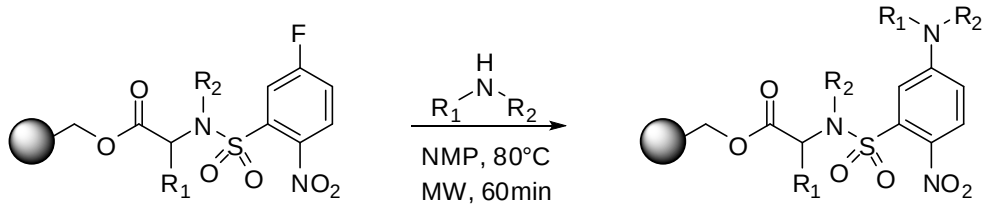
HR-MS (ESI): calculated for [$M\text{-}H^+$] = 363,0843, found 363,0846

^{1}H NMR (300 MHz, Acetone) δ ppm 9.25 (br. s., 1 H) 7.47 - 7.58 (m, 2 H) 7.36 - 7.46 (m, 2 H) 7.24 (d, *J*=5.1 Hz, 1 H) 7.10 (d, *J*=7.3 Hz, 1 H) 4.70 - 4.81 (m, 1 H) 2.78 (s, 3 H) 1.67 - 1.87 (m, 3 H) 0.98 (t, *J*=6.5 Hz, 6 H)

^{13}C NMR: (75 MHz, Acetone-d_6) δ 173.07 (C=O) 140.82 (C) 140.40 (C) 134.75 (C) 132.92 (CH) 131.07 (CH) 128.81 (CH) 125.81 (CH) 124.72 (CH) 122.80 (CH) 112.71 (CH) 56.51 (CH) 37.05 (CH_2) 29.97 (CH_3) 24.66 (CH) 23.77 (CH_3) 21.57 (CH_3) ppm

TLC: R_f = 0,08 (hexane/EtOAc 80/20)

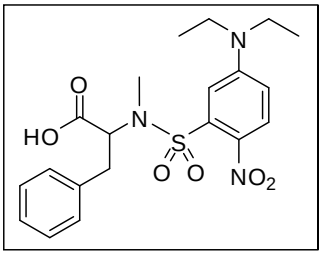
7 ON-RESIN NUCLEOPHILIC AROMATIC SUBSTITUTION



II.133 **II.134**

To the fluoro containing resin **II.133** (0.349 mmol, 1 eq), brought in a microwave tube, is added subsequently 5 ml of NMP and the amine (6.99 mmol, 20 eq). This suspension is heated for 60 min using microwave heating with constant cooling (Powermax method), then filtered off and washed 3x with DMF, MeOH and CH_2Cl_2.

This reaction was optimized for compound **II.134**, with R_1 = Bn and R_2 = Me. LC-MS analysis after cleavage delivered the following result:



Formula: $C_{20}H_{25}N_3O_6S$

Molecular weight: 435,49 g/mol

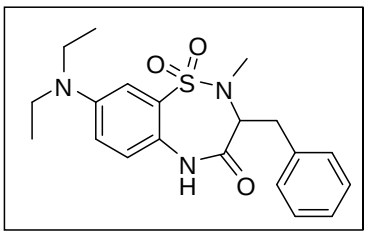
LC-MS:

t_{ret} = 12,7 min

ES-MS [m/z (fragment, intensity)]: 434,0 ($M\text{-}H^+$, 100) 869,2 ($2M\text{-}H^+$, 10)

7.1 SYNTHESIS OF 8-ALKYLAMINO-2,3-DIHYDRO-1,2,5-BENZOTHIADIAZEPIN-4(5*H*)-ONE-1,1-DIOXIDES

7.1.1 3-BENZYL-8-(N-DIETHYLAMINO)-2,3-DIHYDRO-2-METHYL-1,2,5-BENZOTHIADIAZEPIN-4(5*H*)-ONE-1,1-DIOXIDE **II.135-A**



Formula: $C_{20}H_{25}N_3O_3S$

Molecular weight: 387,50 g/mol

Yield: 18%

LC-MS:

t_{ret} = 17,5 min

ES-MS [m/z (fragment, intensity)]: 388,1 ($M+H^+$, 100)

purity: 84%

HR-MS (ESI): calculated for [$M\text{-}H^+$] = 386,1544, found 386,1550

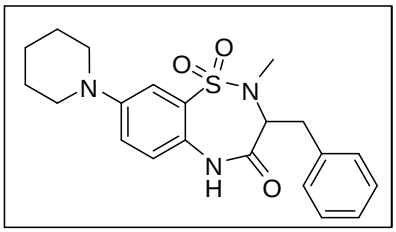
^{1}H NMR: (300 MHz, CHLOROFORM-*d*) δ ppm 8.02 - 8.14 (app d, 1 H) 7.28 - 7.38 (m, 4 H) 7.19 - 7.25 (m, 1 H) 7.03 (d, *J*=3.0 Hz, 1 H) 6.84 (dd, *J*=9.0, 2.8 Hz, 1 H) 6.75 (dd, *J*=9.0, 3.0 Hz, 1 H) 4.55 - 4.66 (m,

1 H) 3.58 (dd, *J*=14.4, 6.1 Hz, 1 H) 3.36 (q, *J*=7.0 Hz, 4 H) 3.09 (dd, *J*=14.4, 8.4 Hz, 1 H) 2.75 (s, 3 H) 1.16 (t, *J*=7.2 Hz, 6 H)

^{13}C NMR: (75 MHz, CHLOROFORM-*d*) δ 170.74 (C=O) 144.77 (C) 137.00 (C) 130.94 (C) 129.41 (CH) 128.49 (CH) 126.73 (CH) 123.10 (CH) 120.54 (C) 116.75 (CH) 109.82 (CH) 61.58 (CH) 44.46 (CH_2) 35.69 (CH_2) 32.44 (CH_3) 12.38 (CH_3) ppm

TLC: R_f = 0,16 (hexane/EtOAc 60/40)

7.1.2 3-BENZYL-2,3-DIHYDRO-2-METHYL-8-(N-PIPERAZINYL)-1,2,5-BENZOTHIADIAZEPIN-4(5*H*)-ONE-1,1-DIOXIDE **II.135-B**



Formula: $C_{21}H_{25}N_3O_3S$

Molecular weight: 399,51 g/mol

Yield: 43%

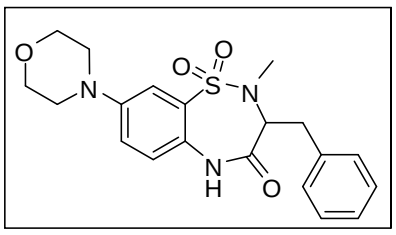
HR-MS (ESI): calculated for [M-H$^+$] = 398,1544, found 398,1550

^{1}H NMR: (300 MHz, CHLOROFORM-*d*) δ ppm 8.34 (br. s., 1 H) 7.28 - 7.39 (m, 5 H) 7.03 (d, *J*=7.9 Hz, 1 H) 6.88 (d, *J*=9.0 Hz, 1 H) 4.64 (dd, *J*=8.6, 5.9 Hz, 1 H) 3.59 (dd, *J*=14.5, 5.8 Hz, 1 H) 3.14 - 3.25 (m, 4 H) 3.09 (dd, *J*=14.5, 8.7 Hz, 1 H) 2.73 (s, 3 H) 1.49 - 1.79 (m, 7 H)

^{13}C NMR: (75 MHz, CHLOROFORM-*d*) δ 171.10 (C=O) 148.60 (C) 136.86 (C) 130.34 (C) 129.35 (CH) 128.52 (CH) 126.76 (CH) 123.51 (C) 122.59 (CH) 121.42 (CH) 114.28 (CH) 61.76 (CH) 49.93 (CH_2) 35.75 (CH_2) 32.43 (CH_3) 25.43 (CH_2) 23.96 (CH_2) ppm

TLC: R_f = 0,28 (hexane/EtOAc 60/40)

7.1.3 3-BENZYL-2,3-DIHYDRO-2-METHYL-8-(N-MORPHOLINO)-1,2,5-BENZOTHIADIAZEPIN-4(5*H*)-ONE-1,1-DIOXIDE **II.135-C**



Formula: $C_{20}H_{23}N_3O_4S$

Molecular weight: 401,48 g/mol

Yield: 39%

LC-MS:

t_{ret} = 15,4 min
ES-MS [m/z (fragment, intensity)]: 400,1 (M-H$^+$, 100)
purity: 99%

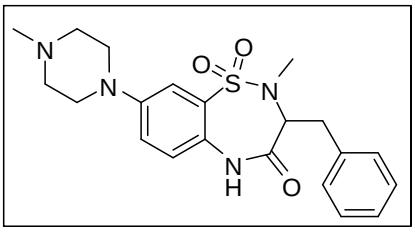
HR-MS (ESI): calculated for [M-H$^+$] = 400,1337, found 400,1336

^{1}H NMR: (300 MHz, CHLOROFORM-*d*) δ ppm 7.28 - 7.38 (m, 5 H) 7.21 - 7.26 (m, 1 H) 6.98 - 7.06 (m, 1 H) 6.90 (d, *J*=8.9 Hz, 1 H) 4.60 - 4.71 (m, 1 H) 3.86 (app t, *J*=4.7 Hz, 4 H) 3.60 (dd, *J*=14.5, 5.8 Hz, 1 H) 3.18 (app t, *J*=4.7 Hz, 4 H) 3.11 (dd, *J*=14.5, 8.7 Hz, 1 H) 2.75 (s, 3 H)

^{13}C NMR: (75 MHz, CHLOROFORM-*d*) δ 171.08 (C=O) 147.81 (C) 136.74 (C) 130.50 (C) 129.33 (CH) 128.55 (CH) 126.83 (CH) 124.50 (C) 122.65 (CH) 120.73 (CH) 114.00 (CH) 65.54 (CH_2) 61.76 (CH) 48.67 (CH_2) 35.72 (CH_2) 32.39 (CH_3) ppm

TLC: R_f = 0,07 (hexane/EtOAc 60/40)

7.1.4 3-BENZYL-2,3-DIHYDRO-2-METHYL-8-(4-METHYLPIPERAZINYL)-1,2,5-BENZOTHIADIAZEPIN-4(5*H*)-ONE-1,1-DIOXIDE **II.135-D**



Formula: $C_{21}H_{26}N_4O_3S$

Molecular weight: 414,52 g/mol

Yield: 32%

LC-MS:

t_{ret} = 14,3 min
ES-MS [m/z (fragment, intensity)]: 413,1 ($M-H^+$, 100)
purity: 99%

HR-MS (ESI): calculated for [$M-H^+$] = 413,1652, found 413,1651

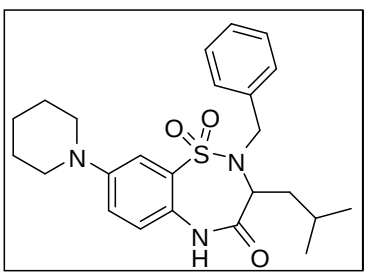
^{1}H NMR: (300 MHz, CHLOROFORM-*d*) δ ppm 7.73 - 8.14 (m, 1 H) 7.26 - 7.37 (m, 5 H) 7.17 - 7.23 (m, 1 H) 7.00 (dd, *J*=8.9, 2.8 Hz, 1 H) 6.84 (t, *J*=8.4 Hz, 1 H) 4.62 (dd, *J*=8.8, 5.9 Hz, 1 H) 3.58 (dd, *J*=14.4, 5.9 Hz, 1 H) 3.21 (app t, *J*=4.9 Hz, 4 H) 3.08 (dd, *J*=14.5, 8.9 Hz, 1 H) 2.72 (s, 3 H) 2.54 (app t, *J*=5.3 Hz, 4 H) 2.34 (s, 3 H)

^{13}C NMR: (75 MHz, CHLOROFORM-*d*) δ 170.85 (C=O) 147.80 (C) 136.76 (C) 130.44 (C) 129.35 (CH) 128.55 (CH) 126.81 (CH) 123.98 (C) 122.54 (CH) 120.82 (CH) 114.19 (CH) 61.76 (CH) 54.71 (CH_2) 48.42 (CH_2) 46.07 (CH_3) 35.70 (CH_2) 32.44 (CH_3)

IR (HATR): 2943 (w) 2831 (w) 2357 (w) 2342 (w) 1687 (m) 1614 (w) 1577 (w) 1499 (m) 1452 (w) 1433 (w) 1404 (w) 1378 (m) 1333 (m) 1302 (w) 1287 (w) 1272 (w) 1246 (m) 1206 (w) 1194 (w) 1162 (m) 1137 (m) 1090 (w) 1060 (vw) 1013 (w) 994 (w) 953 (w) 936 (w) 918 (w) 848 (w) 824 (w) 794 (w) 780 (w) 763 (w) 745 (m) 714 (w) 700 (m) 670 (w) 652 (w) 635 (w)

TLC: R_f = 0,11 (CH_2Cl_2/MeOH 95/5)

7.1.5 2-BENZYL-2,3-DIHYDRO-3-ISOBUTYL-8-(N-PIPERAZINYL)-1,2,5-BENZOTHIADIAZEPIN-4(5*H*)-ONE-1,1-DIOXIDE **II.135-E**



Formula: $C_{24}H_{31}N_3O_3S$

Molecular weight: 441,59 g/mol

Yield: 39%

LC-MS:
t_{ret} = 20,3 min

ES-MS [m/z (fragment, intensity)]: 440,2 ($M-H^+$, 100)
purity: 80%

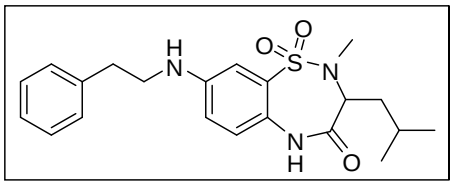
HR-MS (ESI): calculated for [$M-H^+$] = 440,2013, found 440,2017

^{1}H NMR: (300 MHz, CHLOROFORM-*d*) δ ppm 8.14 - 8.54 (m, 1 H) 7.42 - 7.54 (m, 1 H) 7.26 - 7.41 (m, 4 H) 7.12 - 7.24 (m, 1 H) 6.80 - 6.98 (m, 1 H) 4.51 - 4.68 (m, 2 H) 4.05 (d, *J*=15.6 Hz, 1 H) 3.14 - 3.32 (m, 4 H) 1.71 - 1.83 (m, 4 H) 1.46 - 1.71 (m, 5 H) 1.00 (dd, *J*=7.3, 6.1 Hz, 1 H) 0.80 (d, *J*=6.2 Hz, 3 H) 0.56 (d, *J*=6.4 Hz, 3 H)

^{13}C NMR: (75 MHz, CHLOROFORM-*d*) δ 172.69 (C=O) 146.88 (C) 136.26 (C) 131.13 (C) 128.47 (CH) 128.41 (CH) 127.96 (CH) 125.17 (C) 122.90 (CH) 122.62 (CH) 115.31 (CH) 58.30 (CH) 51.21 (CH_2) 50.30 (CH_2) 38.02 (CH_2) 25.06 (CH_2) 23.54 (CH_2) 23.52 (CH) 22.67 (CH_3) 21.03 (CH_3)

TLC: R_f = 0,09 (hexane/EtOAc 75/25)

7.1.6 8-(N-(2-PHENYL)ETHYLAMINO)-2,3-DIHYDRO-3-ISOBUTYL-2-METHYL-1,2,5-BENZOTHIADIAZEPIN-4(5*H*)-ONE-1,1-DIOXIDE **II.135-F**



Formula: $C_{21}H_{27}N_3O_3S$

Molecular weight: 401,52 g/mol

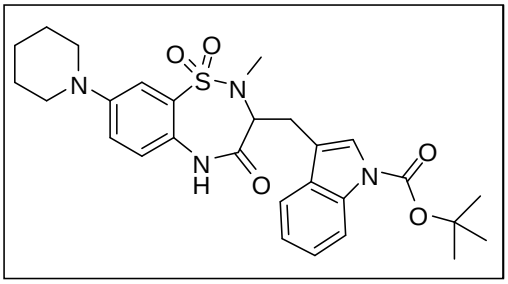
Yield: 35%

LC-MS:
t_{ret} = 17,9 min
ES-MS [m/z (fragment, intensity)]: 400,1 ($M-H^+$, 100)
purity: 94%

^{1}H NMR: (300 MHz, CHLOROFORM-*d*) δ ppm 7.90 (br. s., 1 H) 7.26 - 7.37 (m, 2 H) 7.15 - 7.23 (m, 2 H) 7.05 (d, *J*=2.6 Hz, 1 H) 6.76 (d, *J*=8.5 Hz, 1 H) 6.68 (dd, *J*=8.7, 2.8 Hz, 1 H) 4.57 (dd, *J*=9.6, 4.5 Hz, 1 H) 3.84 (br. s., 1 H) 3.34 - 3.47 (m, 2 H) 2.91 (t, *J*=6.9 Hz, 2 H) 2.78 (s, 3 H) 1.70 - 1.92 (m, 3 H) 0.99 (app t, *J*=6.3 Hz, 6 H)

^{13}C NMR: (75 MHz, CHLOROFORM-*d*) δ 171.85 (C=O) 144.86 (C) 138.57 (C) 130.67 (C) 128.71 (CH) 126.69 (CH) 122.73 (CH) 122.24 (C) 118.70 (CH) 110.65 (CH) 56.90 (CH) 44.81 (CH_2) 36.60 (CH_2) 35.18 (CH_2) 30.38 (CH_3) 28.83 (CH) 23.34 (CH_3) 21.16 (CH_3) ppm

7.1.7 2-BENZYL-2,3-DIHYDRO-3-ISOBUTYL-8-(N-PIPERAZINYL)-1,2,5-BENZOTHIADIAZEPIN-4(5*H*)-ONE-1,1-DIOXIDE **II.135-G**



Formula: $C_{28}H_{34}N_4O_5S$ (white solid)

Molecular weight: 538,66 g/mol

Yield: 41%

LC-MS:
t_{ret} = 20,0 min
ES-MS [m/z (fragment, intensity)]: 537,2 ($M-H^+$, 100)
purity: 86%

HR-MS (ESI): calculated for [$M+H^+$] = 539,2323, found 539,2306; calculated for [$M-H^+$] = 537,2177, found 537,2163

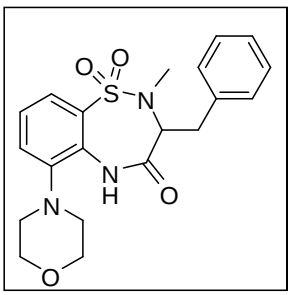
^{1}H NMR: (300 MHz, CHLOROFORM-*d*) δ ppm 8.12 (d, *J*=7.7 Hz, 1 H) 7.82 (br. s., 1 H) 7.66 (s, 1 H) 7.59 (d, *J*=7.3 Hz, 1 H) 7.27 - 7.35 (m, 2 H) 7.17 - 7.24 (m, 1 H) 7.01 (dd, *J*=8.9, 2.8 Hz, 1 H) 6.77 - 6.87 (m, 1 H) 4.76 (t, *J*=6.8 Hz, 1 H) 3.65 (dd, *J*=15.5, 6.1 Hz, 1 H) 3.11 - 3.24 (m, 5 H) 2.74 - 2.83 (m, 3 H) 1.62 - 1.74 (m, 13 H) 1.51 - 1.62 (m, 2 H)

^{13}C NMR: (75 MHz, CHLOROFORM-*d*) δ 170.74 (C=O) 130.36 (C=O) 130.28 (C) 124.57 (CH) 124.41 (CH) 123.13 (C) 122.56 (CH) 121.47 (CH) 118.68 (CH) 115.36 (C) 115.29 (CH) 114.22 (CH) 83.54 (C) 59.58 (CH) 49.86 (CH_2) 32.19 (CH_3) 28.21 (CH_3) 25.45 (CH_2) 25.34 (CH_2) 23.99 (CH_2)

TLC: R_f = 0,68 (pentane/acetone 60/40)

7.2 SYNTHESIS OF 6-ALKYLAMINO-2,3-DIHYDRO-1,2,5-BENZOTHIADIAZEPIN-4(5*H*)-ONE-1,1-DIOXIDES **II.138**

7.2.1 3-BENZYL-2,3-DIHYDRO-2-METHYL-6-(N-MORPHOLINO)-1,2,5-BENZOTHIADIAZEPIN-4(5*H*)-ONE-1,1-DIOXIDE **II.138-A**



Formula: $C_{20}H_{23}N_3O_4S$ (white solid)

Molecular weight: 401,48 g/mol

Yield: 12%

LC-MS:
t_{ret} = 16,5 min
ES-MS [m/z (fragment, intensity)]: 400,1 ($M-H^+$, 100)

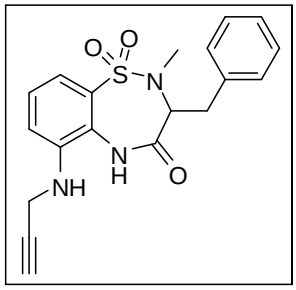
HR-MS (ESI): calculated for [$M+H^+$] = 402,1482, found 402,1478

^{1}H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 9.39 (s, 1 H) 7.72 (dd, *J*=8.0, 1.1 Hz, 1 H) 7.37 (dd, *J*=7.8, 1.2 Hz, 1 H) 7.30 - 7.35 (m, 4 H) 7.20 (t, *J*=7.9 Hz, 1 H) 4.82 - 4.91 (m, 1 H) 3.84 - 3.99 (m, 4 H) 3.63 (dd, *J*=14.7, 5.4 Hz, 1 H) 3.13 (dd, *J*=14.7, 9.5 Hz, 1 H) 2.96 (br. s., 2 H) 2.75 - 2.84 (m, 2 H) 2.72 (s, 3 H)

^{13}C NMR: (125 MHz, CHLOROFORM-*d*) δ 171.10 (C=O) 141.43 (C) 141.41 (C) 136.65 (C) 129.61 (C) 129.22 (CH) 125.71 (CH) 125.38 (CH) 123.81 (CH) 67.20 (CH_2) 61.98 (CH) 52.60 (CH_2) 35.47 (CH_2) 31.80 (CH_3) ppm

TLC: R_f = 0,09 (hexane/EtOAc 60/40)

7.2.2 3-BENZYL-2,3-DIHYDRO-2-METHYL-6-(PROPARGYLAMINO)-1,2,5-BENZOTHIADIAZEPIN-4(5*H*)-ONE-1,1-DIOXIDE **II.138-B**



Formula: $C_{19}H_{19}N_3O_3S$ (white solid)

Molecular weight: 369,44 g/mol

Yield: 7%

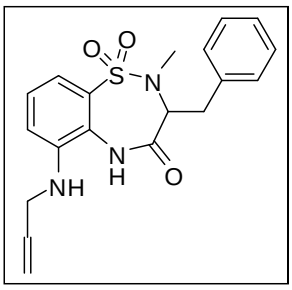
LC-MS:
t_{ret} = 16,3 min
ES-MS [m/z (fragment, intensity)]: 368,0 ($M\text{-}H^+$, 7)

^{1}H NMR ^{1}H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 8.01 (br. s., 1 H) 7.65 (br. s., 1 H) 7.40 (d, *J*=7.8 Hz, 1 H) 7.15 - 7.26 (m, 3 H) 7.07 - 7.15 (m, 1 H) 4.07 (d, *J*=5.6 Hz, 1 H) 3.89 - 4.02 (m, 3 H) 3.55 (dd, *J*=14.2, 6.7 Hz, 1 H) 3.09 (dd, *J*=14.2, 7.3 Hz, 1 H) 2.56 - 2.66 (m, 3 H) 2.25 - 2.31 (m, 1 H)

^{13}C NMR: (75 MHz, Acetone-d_6) δ 170.59 (C=O) 139.05 (C) 136.94 (C) 130.66 (C) 129.56 (CH) 128.55 (CH) 126.81 (CH) 125.76 (CH) 122.07 (C) 118.98 (CH) 118.58 (CH) 79.59 (C) 72.57 (CH_2) 65.16 (CH) 37.15 (CH_2) 35.88 (CH_2) 34.09 (CH_2) ppm

TLC: R_f = 0,17 (hexane/EtOAc 80/20)

7.2.3 3-BENZYL-2,3-DIHYDRO-2-METHYL-6-(PROPENYLYLAMINO)-1,2,5-BENZOTHIADIAZEPIN-4(5*H*)-ONE-1,1-DIOXIDE **II.138-C**



Formula: $C_{19}H_{21}N_3O_3S$ (white solid)

Molecular weight: 371,45 g/mol

Yield: 10%

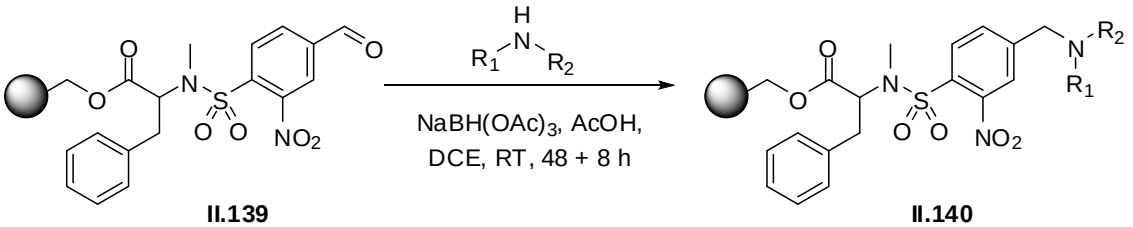
LC-MS:
t_{ret} = 17,1 min
ES-MS [m/z (fragment, intensity)]: 370,1 ($M\text{-}H^+$, 100)

HR-MS (ESI): calculated for [$M\text{-}H^+$] = 370,1231, found 370,1234

[13]C NMR: (75 MHz, Acetone-*d6*) δ 170.42 (C=O) 137.10 (C) 133.89 (CH) 130.53 (C) 129.61 (CH) 128.55 (CH) 126.80 (CH) 125.94 (CH) 121.02 (C) 117.74 (CH) 117.55 (CH_2) 117.45 (C) 65.28 (CH) 46.89 (CH_2) 37.24 (CH_2) 36.10 (CH_3) ppm

TLC: R_f = 0,24 (hexane/EtOAc 80/20)

8 ON-RESIN REDUCTIVE ALKYLATION



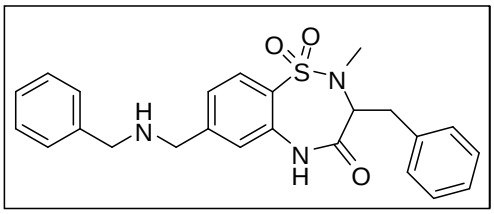
II.139 **II.140**

8.1.1 GENERAL PROCEDURE

To a suspension of formylated resin **II.139** (0.287 mmol, 1 eq) in 14 ml of DCE is added subsequently an amine (1.43 mmol, 5 eq), acetic acid (1.15 mmol, 4 eq) and $NaBH(OAc)_3$ (0.860 mmol, 3 eq). This reaction mixture is shaken for 48 h at room temperature, filtered off and washed 3x with DMF, MeOH and CH_2Cl_2. Applying these reaction conditions for a second time with 8 h of shaking, readily yielded the desired alkylated product **II.140**.

8.2 SYNTHESIS OF 7-ALKYLAMINOMETHYL-2,3-DIHYDRO-1,2,5-BENZOTHIADIAZEPIN-4(5*H*)-ONE-1,1-DIOXIDES **II.141**

8.2.1 3-BENZYL-7-(BENZYLAMINOMETHYL)-2,3-DIHYDRO-2-METHYL-1,2,5-BENZOTHIADIAZEPIN-4(5*H*)-ONE-1,1-DIOXIDE **II.141-A**



Formula: $C_{24}H_{25}N_3O_3S$ (white solid)

Molecular weight: 435,54 g/mol

Yield: 13%

LC-MS:

t_{ret} = 16,6 min
ES-MS [m/z (fragment, intensity)]: 434,1 ($M+H^+$, 100)
Purity: 80%

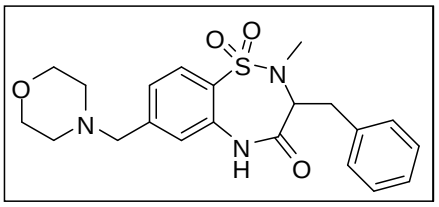
HR-MS (ESI): calculated for [$M-H^+$] = 434,1544, found 434,1547

^{1}H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 8.33 (br. s., 1 H) 7.82 (d, *J*=8.2 Hz, 1 H) 7.26 - 7.37 (m, 9 H) 7.12 - 7.23 (m, 2 H) 7.05 (s, 1 H) 4.65 (dd, *J*=9.1, 5.5 Hz, 1 H) 3.80 (d, *J*=11.8 Hz, 4 H) 3.60 (dd, *J*=14.5, 5.7 Hz, 1 H) 3.10 (dd, *J*=14.5, 9.1 Hz, 1 H) 2.69 (s, 3 H)

^{13}C NMR: (125 MHz, CHLOROFORM-*d*) δ 171.64 (C=O) 147.07 (C) 139.43 (C) 136.64 (C) 132.84 (C) 129.33 (CH) 129.29 (CH) 128.58 (CH) 128.54 (CH) 128.12 (CH) 128.03 (C) 127.29 (CH) 126.86 (CH) 123.86 (CH) 120.44 (CH) 62.21 (CH) 53.15 (CH_2) 51.87 (CH_2) 35.86 (CH) 32.59 (CH_3) ppm

TLC: R_f = 0,14 (CH_2Cl_2/MeOH 97/3)

8.2.2 3-BENZYL-2,3-DIHYDRO-2-METHYL-7-(N-MORPHOLINYLMETHYL)-1,2,5-BENZOTHIADIAZEPIN-4(5*H*)-ONE-1,1-DIOXIDE **II.141-B**



Formula: $C_{22}H_{28}N_4O_3S$ (white solid)

Molecular weight: 415,51 g/mol

Yield: 20%

LC-MS:

t_{ret} = 15,4 min
ES-MS [m/z (fragment, intensity)]: 414,1 ($M+H^+$, 100)
Purity: 93%

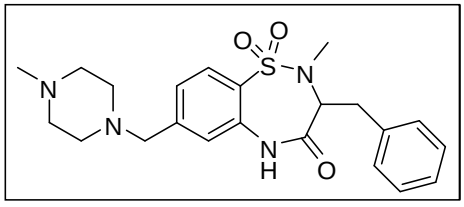
HR-MS (ESI): calculated for [$M-H^+$] = 414,1493, found 414,1495

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 7.83 (d, *J*=8.1 Hz, 1 H) 7.76 (s, 1 H) 7.26 - 7.35 (m, 5 H) 7.17 (d, *J*=8.1 Hz, 1 H) 6.96 (s, 1 H) 4.68 (dd, *J*=9.0, 5.7 Hz, 1 H) 3.70 (t, *J*=4.7 Hz, 4 H) 3.60 (dd, *J*=14.5, 5.7 Hz, 1 H) 3.48 (s, 2 H) 3.11 (dd, *J*=14.5, 9.0 Hz, 1 H) 2.72 (s, 3 H) 2.43 (t, *J*=4.5 Hz, 4 H)

^{13}C NMR: (75 MHz, CHLOROFORM-*d*) δ 171.25 (C=O) 132.58 (C) 129.38 (CH) 129.33 (CH) 128.60 (CH) 126.91 (CH) 124.69 (CH) 120.90 (CH) 66.89 (CH_2) 62.20 (CH_2) 61.92 (CH) 53.62 (CH_2) 35.74 (CH_2) 32.40 (CH_3) ppm

TLC: R_f = 0,13 (CH_2Cl_2/aceton 80/20)

8.2.3 3-BENZYL-2,3-DIHYDRO-2-METHYL-7-(N-(4-METHYLPIPERAZINYL))-1,2,5-BENZOTHIADIAZEPIN-4(5*H*)-ONE-1,1-DIOXIDE **II.141-C**



Formula: $C_{21}H_{25}N_3O_4S$ (white solid)

Molecular weight: 428,55 g/mol

Yield: 22%

LC-MS:

t_{ret} = 13,8 min
ES-MS [m/z (fragment, intensity)]: 427,1 ($M-H^+$, 100)
Purity: 92%

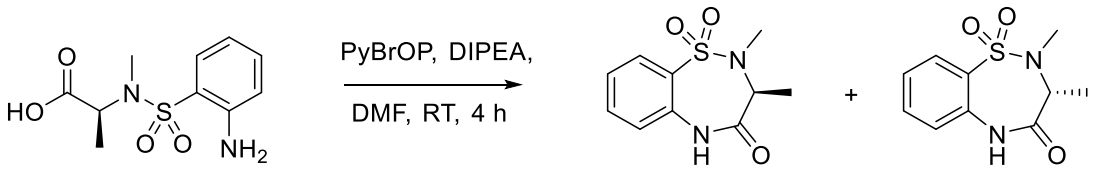
HR-MS (ESI): calculated for [$M-H^+$] = 427,1809, found 427,1812

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 8.45 (br. s., 1 H) 7.81 (d, *J*=8.1 Hz, 1 H) 7.26 - 7.36 (m, 4 H) 7.19 - 7.24 (m, 1 H) 7.16 (d, *J*=8.1 Hz, 1 H) 7.04 (br. s., 1 H) 4.65 (dd, *J*=8.7, 5.7 Hz, 1 H) 3.60 (dd, *J*=14.5, 5.7 Hz, 1 H) 3.10 (dd, *J*=14.5, 9.0 Hz, 1 H) 2.68 (s, 3 H) 2.50 (br. s., 7 H) 2.31 (s, 3 H)

^{13}C NMR: (75 MHz, CHLOROFORM-*d*) δ 171.62 (C=O) 145.32 (C) 136.61 (C) 132.80 (C) 129.32 (CH) 128.57 (CH) 128.21 (C) 126.87 (CH) 124.57 (CH) 121.14 (CH) 62.16 (CH_2) 62.20 (CH_2) 61.92 (CH) 53.62 (CH_2) 35.74 (CH_2) 32.40 (CH_3) ppm

TLC: R_f = 0,04 (CH_2Cl_2/aceton/Et_3N 80/20/1)

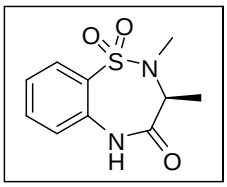
9 OPTICAL PURITY OF THE 2,3-DIHYDRO-1,2,5-BENZOTHIADIAZEPIN-4(5*H*)-ONE-1,1-DIOXIDES



(S)-II.143 **(S)-II.7n**; 99,5% **(R)-II.7n**; 0,5%

9.1.1 PROCEDURE

To the carboxylic acid **(S)-II.143** (9.1 mg, 0.035 mmol, 1 eq), dissolved in 0.500 ml DMF, is added consecutively DIPEA (0.031 ml, 0.176 mmol, 5 eq) and PyBrOP (0.041 mg, 0.082 mmol, 2.5 eq). This reaction mixture is allowed to stir for 4 h, before it is poured into a seperating funnel together with 4 ml of a 1 M HCl solution. This suspension is extracted 3x with 2.5 ml of EtOAc, the collected organic phases washed with 5 ml of brine, dried over $MgSO_4$ and evaporated under reduced pressure. This crude colorless oil is subsequently purified using column chromatography (eluent hexane/ethylacetate 70/30), readily delivering the desired (3S)-2,3-dihydro-2,3-dimethyl-1,2,5-benzothiadiazepin-4-one-1,1-dioxide **II.7n**.



Formula: $C_{10}H_{12}N_2O_3S$ (white solid)

Molecular weight: 240,28 g/mol

LC-MS:
t_{ret} = 13,0 min
ES-MS [m/z (fragment, intensity)]: 239,0 ($M\text{-}H^+$, 100)

^{1}H NMR (300 MHz, CHLOROFORM-d) δ 8.30 (br. s., 1 H) 7.96 (dd, *J*=7.9, 1.5 Hz, 1 H) 7.52 (ddd, *J*=8.1, 7.4, 1.6 Hz, 1 H) 7.22 - 7.32 (m, 4 H) 7.02 (d, *J*=8.1 Hz, 1 H) 4.62 - 4.76 (m, 1 H) 2.82 (s, 3 H) 1.60 (d, *J*=7.0 Hz, 3 H) ppm

^{13}C NMR: (75 MHz, CHLOROFORM-*d*) δ 172.65 (C) 133.77 (CH) 132.66 (C) 129.37 (CH) 129.19 (C) 121.30 (CH) 121.21 (CH) 55.65 (CH) 31.01 (CH_3) 15.28 (CH_3) ppm

TLC: R_f = 0,15 (hexane/EtOAc 60/40)

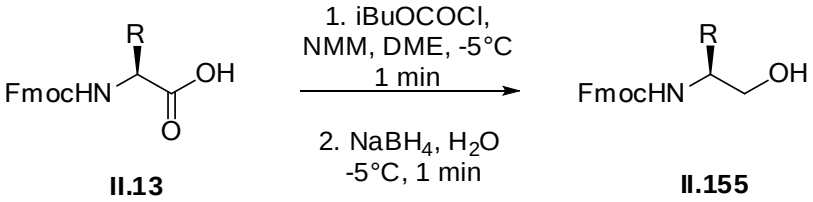
Chiral LC:

Column & eluent: Chiralpak IA, 30 min isocratic n-hexane/Ethanol 60/40
t_{ret}(**(S)-II.7n**) = 6,8 min; t_{ret}(**(R)-II.7n**) = 11,1 min
Enantiomeric ratio: (3S)/(3R) 99,5/0,5

Optical rotation: $[\alpha]_D^{20}$ = +36° (c = 0.2, $CHCl_3$)

10 SYNTHESIS OF β-AMINOETHANESULFONYL CHLORIDES

10.1 SYNTHESIS OF THE Nα-FMOC-2-AMINOETHANOLS **II.155-(a-c)**

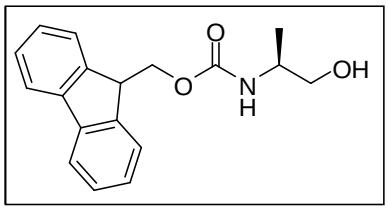


II.13 **II.155**

10.1.1 GENERAL PROCEDURE

The Fmoc-protected α-amino acid **II.13-(a-c)** (52.0 mmol, 1.00 eq) is soluted in 80 ml DME and cooled down to -5°C. Subsequently, isobutyl chloroformate (6.78 ml, 52.0 mmol, 1.00 eq) and NMM (5.76 ml, 52.0 mmol, 1.00 eq) are added and this mixture is stirred for 1 min. The formed NMM salt is then filtered off and washed with DME, while the filtrate is caught in a flask and cooled again to -5°C. To this filtrate, a solution of $NaBH_4$ (2.95 g, 78.0 mmol, 1.50 eq) in 40 ml of water is added very carefully (extensive CO_2 formation) over a period of 1 min. When there is no more visible evolution of CO_2 from the reaction mixture, the reaction is quenched with 200 ml of water. The formed white precipitate is then filtered off, washed thoroughly with water and freeze dried to obtain the pure aminoalcohol **II.155-(a-c)**.

10.1.2 (S)-Nα-FMOC-L-ALANINOL **II.155-A**



Yield: 94% (white powder)

Formula: $C_{18}H_{19}NO_3$

Molecular weight: 297,17 g/mol

LC-MS:

t_{ret} = 15,7 min
ES-MS [m/z (fragment, intensity)]: 298,1 ($M+H^+$, 100)

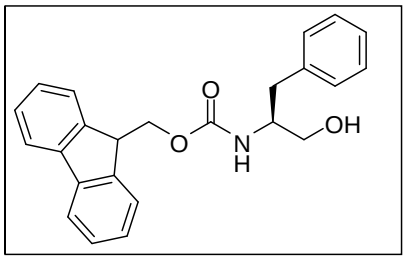
^{1}H NMR (300 MHz, CHLOROFORM-d) δ 7.70 (d, *J*=7.35 Hz, 2 H) 7.52 (d, *J*=7.35 Hz, 2 H) 7.33 (t, *J*=7.54 Hz, 2 H) 7.25 (t, *J*=7.35 Hz, 2 H) 4.88 - 4.69 (m, 1 H) 4.36 (d, *J*=6.40 Hz, 2 H) 4.14 (t, *J*=6.78 Hz, 1 H) 3.84 - 3.68 (m, 1 H) 3.66 - 3.35 (m, 2 H) 1.97 (s, 1 H) 1.10 (d, *J*=6.59 Hz, 3 H) ppm

^{13}C NMR: (75 MHz, CHLOROFORM-d) δ 159.82 (C) 143.85 (C) 141.34 (C) 127.69 (CH) 127.05 (CH) 124.96 (CH) 119.98 (CH) 66.89 (CH_2) 66.67 (CH_2) 48.97 (CH) 47.27 (CH) 17.25 (CH_3) ppm

TLC: R_f = 0,24 (CH_2Cl_2/EtOAc 80/20)

Optical rotation: $[\alpha]_D^{20}$ = -1,1° (c = 1.05, $CHCl_3$)

10.1.3 (S)-N$^{\alpha}$-FMOC-L-PHENYLALANINOL **II.155-B**



Yield: 96% (white powder)

Formula: $C_{24}H_{23}NO_3$

Molecular weight: 373,17 g/mol

LC-MS:

t_{ret} = 17,5 min

ES-MS [m/z (fragment, intensity)]: 374,1 ($M+H^+$, 100)

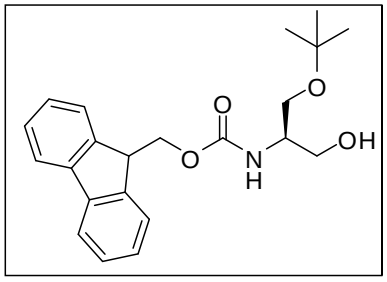
^{1}H NMR: (500 MHz, CHLOROFORM-d) δ 7.77 (d, *J*=7.57 Hz, 2 H) 7.55 (t, *J*=7.09 Hz, 2 H) 7.41 (t, *J*=7.41 Hz, 2 H) 7.35 - 7.28 (m, 4 H) 7.27 - 7.17 (m, 3 H) 4.95 (br. s, 1 H) 4.41 (dd, *J*=16.32, 6.86 Hz, 2 H) 4.20 (t, *J*=6.70 Hz, 1 H) 3.94 (br. s, 1 H) 3.70 (A-deel AB-systeem, d, *J*=8.51 Hz, 1 H) 3.60 (B-deel AB-systeem, d, *J*=8.50 Hz, 1 H) 2.88 (d, *J*=4.57 Hz, 2 H) 1.60 (br. s, 2 H) ppm

^{13}C NMR: (75 MHz, CHLOROFORM-d) δ 143.87 (C) 143.85 (C) 141.34 (C) 137.53 (C) 129.23 (CH) 128.65 (CH) 127.69 (CH) 127.04 (CH) 126.68 (CH) 125.01 (CH) 119.97 (CH) 66.62 (CH_2) 63.99 (CH_2) 54.11 (CH) 47.27 (CH) 37.30 (CH_2)

TLC: R_f = 0,27 (CH_2Cl_2/EtOAc 80/20)

Optical rotation: $[\alpha]_D^{20}$ = -23° (c = 0.85, $CHCl_3$)

10.1.4 (R)-N$^{\alpha}$-FMOC-O-*TERT*-BUTYL-L-SERINOL **II.155-C**



Yield: 75% (white powder)

Formula: $C_{22}H_{27}NO_4$

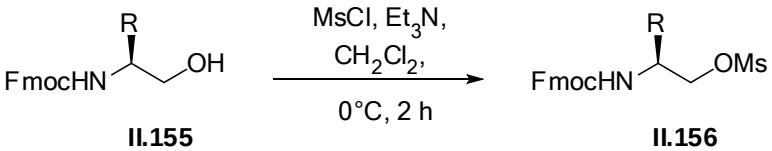
Molecular weight: 369,45 g/mol

^{1}H NMR: (300 MHz, CHLOROFORM-*d*) δ ppm 7.77 (d, *J*=7.5 Hz, 1 H) 7.61 (d, *J*=7.3 Hz, 1 H) 7.36 - 7.45 (m, 1 H) 7.28 - 7.36 (m, 1 H) 5.53 (d, *J*=7.0 Hz, 1 H) 4.40 (d, *J*=7.0 Hz, 2 H) 4.24 (t, *J*=6.8 Hz, 1 H) 3.67 - 3.96 (m, 3 H) 3.62 (d, *J*=2.3 Hz, 2 H) 2.92 (br. s., 1 H)

^{13}C NMR: (75 MHz, CHLOROFORM-d) δ 156.33 (COONH) 143.93 (C) 141.29 (C) 127.66 (CH) 127.02 (CH) 125.05 (CH) 119.95 (CH) 73.84 (C) 66.79 (CH_2) 64.72 (CH_2) 63.81 (CH_2) 51.54 (CH) 47.22 (CH) 27.33 (CH_3)

TLC: R_f = 0,10 (CH_2Cl_2/EtOAc 90/10)

10.2 Nα-FMOC-2-AMINOETHANEMESYLATES

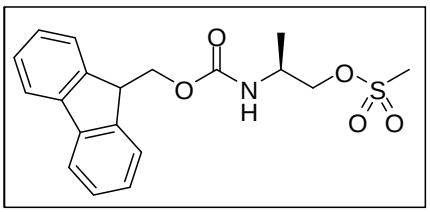


II.155 **II.156**

10.2.1 GENERAL PROCEDURE

The aminoalcohol **II.155** (34.6 mmol, 1.00 eq) is soluted in 120 ml of dichloromethane and cooled to 0°C, followed by addition of Et_3N (5.78 ml, 41.5 mmol, 1.20 eq) and mesyl chloride. This reaction mixture is subsequently stirred for 2 h while allowed to warm up to room temperature. Then it is poured into a seperating funnel and washed successively with 200 ml of a saturated NaHCO3 solution, 200 ml of water and 100 ml of brine. The organic phase is then evaporated under reduced pressure, yielding a yellowish oil, which is then recrystallized in a mixture of dichloromethane and hexane to deliver the desired mesylates **II.156**.

10.2.2 (S)-Nα-FMOC-3-AMINO-METHYLETHANEMETHYLSULFONATE **II.156-A**



Yield: 80% (white crystals)

Formula: $C_{19}H_{21}NO_5S$

Molecular weight: 375,11 g/mol

LC-MS:

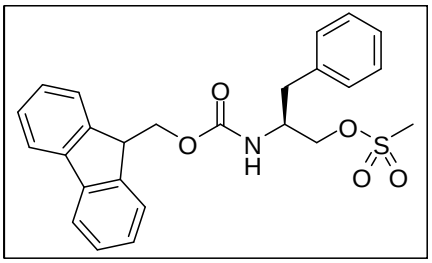
t_{ret} = 16,9 min
ES-MS [m/z (fragment, intensity)]: 376,1 ($M+H^+$, 80), 198,0 ($M+H^+$-Fm, 100), 179,1 (dibenzofulvene+H^+, 60), 154,0 ($M+H^+$-Fm-CO_2, 70)

^{1}H NMR: (300 MHz, CHLOROFORM-*d*) δ 7.79 (d, *J*=7.54 Hz, 2 H) 7.61 (d, *J*=7.16 Hz, 2 H) 7.48 - 7.39 (m, 2 H) 7.39 - 7.30 (m, 2 H) 4.90 (br. s, 1 H) 4.58 - 4.33 (m, 2 H) 4.32 – 3.94 (m, 3 H) 3.11 – 2.88 (m, 2 H) 1.29 (d, *J*=5.46 Hz, 3 H) ppm

^{13}C NMR: (75 MHz, CHLOROFORM-d) δ 155.58 (C) 143.78 (C) 141.34 (C) 127.75 (CH) 127.09 (CH) 124.97 (CH) 120.01 (CH) 71.73 (CH) 66.80 (CH_2) 47.20 (CH) 46.14 (CH) 37.39 (CH_3) 17.15 (CH_3) ppm

TLC: R_f = 0,58 (CH_2Cl_2/EtOAc 80/20)

10.2.3 (S)-Nα-FMOC-3-AMINO-BENZYLETHANEMETHYLSULFONATE **II.156-B**



Yield: 86% (white crystals)

Formula: $C_{25}H_{25}NO_5S$ (VDM/01/27)

Molecular weight: 451,15 g/mol

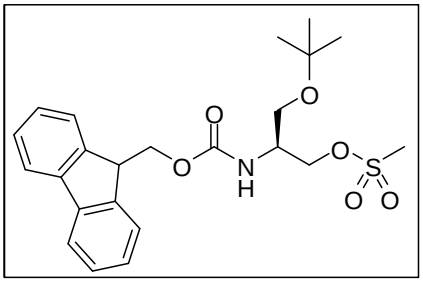
LC-MS:
t_{ret} = 18,3 min
ES-MS [m/z (fragment, intensity)]: 452,0 ($M+H^+$, 100)

^{1}H NMR: (300 MHz, CHLOROFORM-d) δ 7.78 (d, *J*=7.54 Hz, 2 H) 7.56 (dd, *J*=7.35, 3.77 Hz, 2 H) 7.46 - 7.37 (m, 2 H) 7.37 - 7.28 (m, 4 H) 7.26 - 7.17 (m, 3 H) 4.97 (br. s, 1 H) 4.41 (d, 6.8 Hz, 2 H) 4.32 - 4.25 (m, 2 H) 4.21 (t, *J*=6.03 Hz, 2 H) 3.00 (s, 3 H) 2.96 - 2.84 (m, 2 H) ppm

^{13}C NMR: (75 MHz, CHLOROFORM-d) δ 155.64 (C) 143.73 (C) 141.31 (C) 136.30 (C) 129.20 (CH) 128.83 (CH) 127.74 (CH) 127.09 (CH) 125.01 (CH) 120.00 (CH) 69.59 (CH_2) 66.84 (CH_2) 51.40 (CH) 47.15 (CH) 37.33 (CH_3) 37.30 (CH_2)

TLC: R_f = 0,67 (CH_2Cl_2/EtOAc 80/20)

10.2.4 (S)-N$^\alpha$-FMOC-3-AMINO-(*TERT*-BUTOXYMETHYL)ETHANEMETHYL-SULFONATE **II.156-C**



Yield: 99% (white solid)

Formula: $C_{23}H_{29}NO_6S$

Molecular weight: 447,54 g/mol

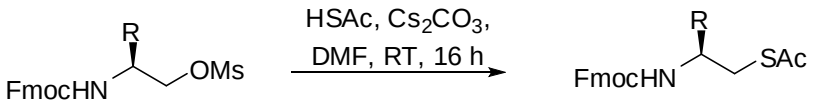
LC-MS:
t_{ret} = 18,7 min
ES-MS [m/z (fragment, intensity)]: 392,1 ($M+H^+$-tBu, 10), 214,0 ($M+H^+$-tBu-dibenzofulveen, 20), 179,1 (dibenzofulvene+H^+, 25) 170,0 ($M+H^+$-tBu-dibenzofulveen-CO_2, 45)

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 7.77 (d, *J*=7.3 Hz, 2 H) 7.59 (d, *J*=7.3 Hz, 2 H) 7.41 (t, *J*=7.0 Hz, 2 H) 7.32 (t, *J*=7.3 Hz, 2 H) 5.19 (d, *J*=8.1 Hz, 1 H) 4.36 - 4.53 (m, 1 H) 4.17 - 4.35 (m, 2 H) 4.06 (br. s., 1 H) 3.33 - 3.61 (m, 2 H) 3.01 (s, 3 H) 1.19 (s, 9 H)

^{13}C NMR: (75 MHz, CHLOROFORM-d) δ 155.85 (COONH) 143.74 (C) 141.30 (C) 127.74 (CH) 127.06 (CH) 124.98 (CH) 120.01 (CH) 73.56 (C) 67.97 (CH_2) 66.93 (CH_2) 59.52 (CH) 50.00 (CH) 47.16 (CH) 37.27 (CH_3) 27.36 (CH_3)

TLC: R_f = 0,45 (CH_2Cl_2/EtOAc 90/10)

10.3 N$^\alpha$-FMOC-AMINOETHAANTHIOACETATEN **II.157**

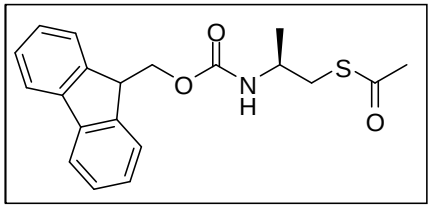


II.156-(a-c) **II.157-(a-c)**

10.3.1 GENERAL PROCEDURE

A solution of the mesylate **II.X** (33.5 mmol, 1.00 eq) in 50 ml DMF is added to a stirred emulsion of Cs_2CO_3 and HSAc in 175 ml DMF. The orange reaction mixture is then stirred further for 16 h while the flask is wrapped in aluminum foil. Subsequently, this mixture was poured into a seperating funnel together with 1000 ml of water and extracted 3 times with 500 ml of EtOAc. The combined organic phases are then washed with 700 ml water, 700 ml of 5% $NaHCO_3$ solution, 350 ml of brine followed by drying over MgSO4. This crude mixture is then evaporated under reduced pressure and purified by flash chromatography.

10.3.2 (S)-N$^{\alpha}$-FMOC-2-AMINO-METHYLETHANETHIOACETATE **II.157-A**



Yield: 62%

Formula: $C_{20}H_{21}NO_3S$

Molecular weight: 355,12 g/mol

LC-MS:

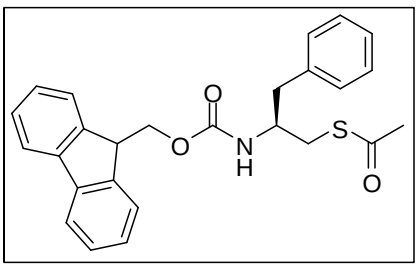
t_{ret} = 18,2 min
ES-MS [m/z (fragment, intensity)]: 356,1 ($M+H^+$, 15), 179,1 (dibenzofulvene+H^+, 55), 134,1 ($M+H^+$-Fmoc, 30)

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ 7.69 (d, *J*=7.35 Hz, 2 H) 7.51 (d, *J*=7.35 Hz, 2 H) 7.33 (t, *J*=7.16 Hz, 2 H) 7.24 (t, *J*=7.35 Hz, 4 H) 4.80 (d, *J*=6.22 Hz, 1 H) 4.39 - 4.21 (m, 2 H) 4.14 (t, *J*=6.59 Hz, 1 H) 3.85 (m, 1 H) 2.99 (d, *J*=5.46 Hz, 2 H) 2.28 (s, 3 H) 1.15 (d, *J*=6.40 Hz, 3 H) ppm

^{13}C NMR: (75 MHz, CHLOROFORM-d) δ 155.64 (C) 143.93 (C) 141.30 (C) 127.65 (CH) 127.01 (CH) 125.05 (CH) 119.95 (CH) 77.20 (CH) 66.64 (CH_2) 47.24 (CH) 34.82 (CH) 30.57 (CH_3) 20.24 (CH_3) ppm

TLC: R_f = 0,13 (hexane/EtOAc 80/20)

10.3.3 (S)-N$^{\alpha}$-FMOC-2-AMINO-BENZYLETHANETHIOACETATE **II.157-B**



Yield: 56%

Formula: $C_{26}H_{25}NO_3S$

Molecular weight: 431,16 g/mol

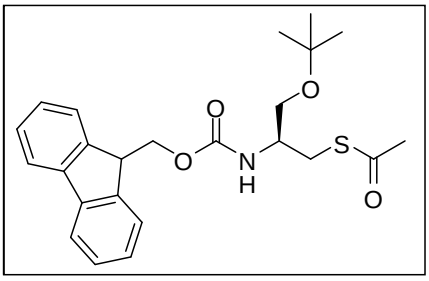
LC-MS:
t_{ret} = 19,4 min
ES-MS [m/z (fragment, intensity)]: 432,2 ($M+H^+$, 15), 254,1 ($M+H^+$-Fm, 15) 210,1 ($M+H^+$-Fmoc, 35), 179,1 (dibenzofulvene+H^+, 35)

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ 7.78 (d, *J*=7.54 Hz, 2 H) 7.56 (d, *J*=7.54 Hz, 2 H) 7.41 (t, *J*=7.54 Hz, 2 H) 7.37 - 7.27 (m, 4 H) 7.26 - 7.14 (m, 3 H) 4.94 (d, *J*=8.10 Hz, 1 H) 4.60 - 4.25 (m, 2 H) 4.20 (t, *J*=6.78 Hz, 1 H) 4.15 – 3.97 (m, 1 H) 3.15 – 2.77 (m, 4 H) 2.37 (s, 3 H) ppm

^{13}C NMR: (75 MHz, CHLOROFORM-*d*) δ 155.74 (C) 143.91 (C) 141.32 (C) 137.03 (C) 129.37 (CH) 128.64 (CH) 127.68 (CH) 127.04 (CH) 126.80 (CH) 125.15 (CH) 125.08 (CH) 119.98 (CH)66.69 (CH_2) 52.66 (CH) 47.22 (CH) 40.53 (CH_2) 32.65 (CH_2) 30.63 (CH_3) ppm

TLC: R_f = 0,58 (hexane/EtOAc 80/20)

10.3.4 (S)-N$^{\alpha}$-FMOC-2-AMINO-(*TERT*-BUTOXYMETHYL)ETHANETHIOACETATE **II.157-C**



Yield: 77%

Formula: $C_{24}H_{29}NO_4S$

Molecular weight: 427,56 g/mol

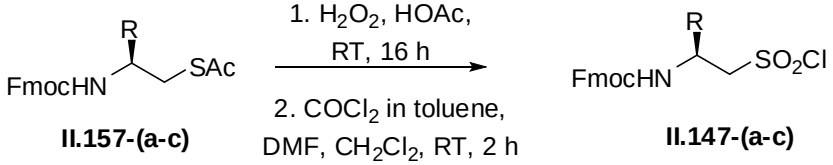
LC-MS:
t_{ret} = 20,0 min
ES-MS [m/z (fragment, intensity)]: 428,1 ($M+H^+$, 5), 372,1 ($M+H^+$-tBu, 30), 194,0 ($M+H^+$-tBu-dibenzofulveen, 15), 179,1 (dibenzofulvene+H^+, 30) 150,1 ($M+H^+$-tBu-dibenzofulveen-CO_2, 20)

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 7.77 (d, *J*=7.3 Hz, 2 H) 7.60 (d, *J*=7.2 Hz, 2 H) 7.36 - 7.45 (m, 2 H) 7.28 - 7.36 (m, 2 H) 5.22 (d, *J*=8.3 Hz, 1 H) 4.29 - 4.46 (m, 2 H) 4.24 (t, *J*=6.8 Hz, 1 H) 3.91 (br. s., 2 H) 3.31 - 3.56 (m, 2 H) 3.15 (d, *J*=6.8 Hz, 1 H) 2.35 (s, 3 H) 1.18 (s, 9 H)

^{13}C NMR: (75 MHz, CHLOROFORM-d) δ 155.95 (COONH) 143.94 (C) 141.28 (C) 127.64 (CH) 127.01 (CH) 125.12 (CH) 119.95 (CH) 73.23 (C) 66.78 (CH_2) 62.54 (CH_2) 51.36 (CH) 47.21 (CH) 30.98 (CH_2) 30.58 (CH_3) 27.42 (CH_3)

TLC: R_f = 0,09 (pentaan/EtOAc 90/10)

10.4 SYNTHESIS OF N-FMOC-2-AMINOETHANESULFONYL CHLORIDES **II.147**



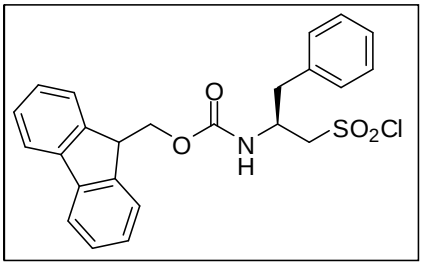
II.157-(a-c) **II.147-(a-c)**

10.4.1 GENERAL PROCEDURE

To an stirring emulsion of thioacetate **II.157-(a-c)** (35.7 mmol, 1.00 eq) in 40 ml AcOH is added a mixture of 40 ml H_2O_2 and 80 ml AcOH in one portion. After 16h stirring, NaOAc (3.22 g, 39.3 mmol, 1.10 eq) is added and the reaction is stirred further for 1 h. Now, the excess of peroxide is destroyed by stirring the reaction mixture for 1 h in the presence of a small amount of Pd/C (10% wt). The sodium sulfonate salt is finally obtained by filtration of this reaction mixture over celite and evaporation of the filtrate under reduced pressure. After freeze-drying for 2 days, the sulfonate salt is emulsified again in 350 ml CH_2Cl_2 and 67.5 ml of a solution of phosgene in toluene (20% v/v) is added together with 10 ml

of DMF. This mixture is stirred for 2h at room temperature, then evaporated under reduced pressure and purified using flash chromatography, yielding the desired sulfonyl chlorides **II.147-(a-c)**.

10.4.2 (S)-N-FMOC-2-AMINO-2-BENZYLETHANESULFONYL CHLORIDE **II.147-A**



Yield: 81% (white solid)

Formula: $C_{24}H_{22}ClNO_4S$

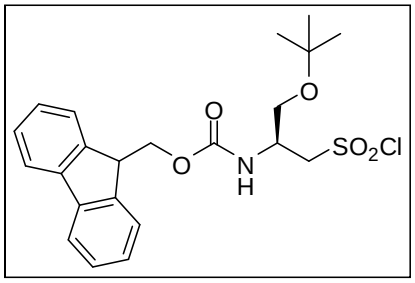
Molecular weight: 455,10 g/mol

LC-MS:
t_{ret} = 19,1 min
ES-MS [m/z (fragment, intensity)]: 454,1 (M-H^+, 55), 436,1 (M-H^+-Cl+OH, 45)

^{1}H NMR: (300 MHz, CHLOROFORM-*d*) δ 7.78 (d, *J*=7.54 Hz, 2 H) 7.56 (d, *J*=7.54 Hz, 2 H) 7.41 (t, *J*=7.54 Hz, 2 H) 7.37 - 7.27 (m, 4 H) 7.26 - 7.14 (m, 3 H) 5.49 (s, 1 H) 4.49 - 4.35 (m, 1 H) 4.34 – 3.98 (m, 5 H) 2.97 (d, *J*=7.16 Hz, 2 H) ppm

TLC: R_f = 0,44 (hexane/EtOAc 60/40)

10.4.3 (S)-N-FMOC-2-AMINO-2-(*TERT*-BUTOXYMETHYL)ETHANESULFONYL CHLORIDE **II.147-B**



Yield: 67% (white solid)

Formula: $C_{22}H_{26Cl}NO_5S$

Molecular weight: 451,96 g/mol

LC-MS:
t_{ret} = 7,3 min
ES-MS [m/z (fragment, intensity)]: 452,0 (M+H^+, 7), 386,0 (M+H^+-*t*Bu, 18), 218,0 (M+H^+-*t*Bu-Fm, 10), 179,1 (dibenzofulvene+H^+, 35) 174,0 (M+H^+-tBu-Fmoc, 25) 156,0 (M+H^+-*t*Bu-Fmoc-Cl+OH, 5)

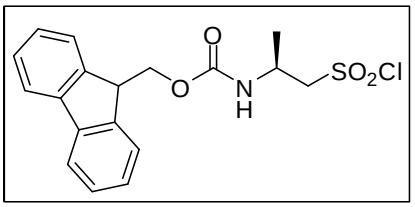
^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 7.77 (d, *J*=7.3 Hz, 2 H) 7.59 (dd, *J*=7.3, 0.9 Hz, 2 H) 7.37 - 7.46 (m, 2 H) 7.32 (td, *J*=7.3, 1.1 Hz, 2 H) 5.33 (d, *J*=7.9 Hz, 1 H) 4.39 - 4.54 (m, 3 H) 4.24 (t, *J*=6.4 Hz, 1 H) 3.99 (d, *J*=4.5 Hz, 2 H) 3.49 - 3.72 (m, 2 H) 1.20 (s, 9 H)

^{13}C NMR: (75 MHz, CHLOROFORM-*d*) δ 155.40 (COONH) 143.66 (C) 141.36 (C) 127.80 (CH) 127.10 (CH) 124.94 (CH) 120.05 (CH) 73.97 (C) 67.02 (CH_2) 65.39 (CH_2) 61.41 (CH_2) 48.21 (CH) 47.21 (CH) 27.41 (CH_3) ppm

TLC: R_f = 0,80 (CH_2Cl_2/EtOAc 80/20)

Optical rotation: $[\alpha]_D^{20}$ = + 23° (c = 1.0, $CHCl_3$)

10.4.4 (S)-N-FMOC-2-AMINO-2-METHYLETHANESULFONYL CHLORIDE **II.147-C**



Yield: 71% (white solid)

Formula: $C_{18}H_{18}ClNO_4S$

Molecular weight: 379,86 g/mol

LC-MS:

t_{ret} = 18,0 min

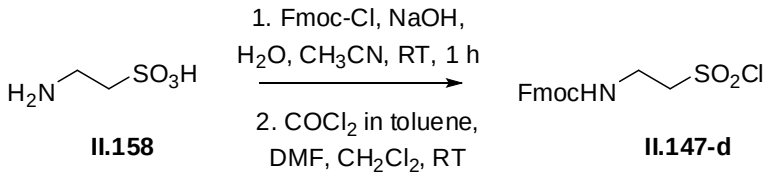
ES-MS [m/z (fragment, intensity)]: 380,0 ($M+H^+$, 12), 202,0 ($M+H^+$-Fm, 25), 179,1 (dibenzofulvene+H^+, 60), 158,0 ($M+H^+$-Fm-CO_2, 3)

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ 7.70 (d, *J*=7.35 Hz, 2 H) 7.51 (d, *J*=7.35 Hz, 2 H) 7.39- 7.21 (m, 4 H) 4.98 (br. s, 1 H) 4.52 - 4.19 (m, 3 H) 4.15 (t, *J*=6.59 Hz, 1 H) 4.10 – 3.96 (m, 1 H) 3.84 - 3.68 (m, 1 H) 1.52 - 1.30 (m, 3 H) ppm

^{13}C NMR: (75 MHz, CHLOROFORM-*d*) δ 155.24 (C=O), 143.78(C), 143.65 (CH), 141.35 (CH), 127.81 (CH), 127.14 (CH), 125.01 (CH), 120.02 (CH), 69.47 (CH_2), 66.88 (CH_2), 47.21 (CH), 44.43 (CH), 19.63 (CH_3)

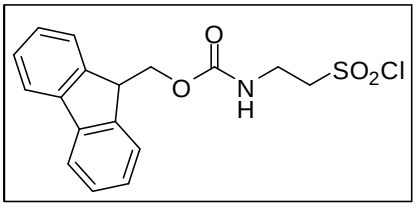
Optical rotation: $[\alpha]_D^{20}$ = + 7° (c = 1.0, $CHCl_3$)

10.4.5 N-FMOC-2-AMINOETHANESULFONYL CHLORIDE



II.158 **II.147-d**

After taurine **II.158** (3.13 g, 25.0 mmol, 1.00 eq) is soluted in 50 ml of water, the pH of this solution is brought to 8.5 by adding a 1M solution of NaOH. Subsequently, a solution of Fmoc chloride (7.79 g, 30.0 mmol, 1.20 eq) in 100 ml CH_3CN is added dropwise while the pH is retained at 8.5 by adding more of the 1M NaOH solution. This reaction mixture is then stirred for 1 h before it is quenched with 150 ml of water. The acquired suspension is extracted 2 times with 200 ml of EtOAc, evaporated under reduced pressure and freeze-dryed for 2 days, delivering the sulfonate salt. Thereafter, the salt is suspended in 200 ml CH_2Cl_2 followed by the addition of 20 ml of a phosgene solution in toluene (20% v/v) and 3 ml of DMF. This suspension is stirred for 1 h at room temperature, evaporated under reduced pressure and purified using column chromatography, delivering the desired sulfonyl chloride **II.147-d**.



Yield: 80%

Formula: $C_{17}H_{16}ClNO_4S$

Molecular weight: 365,05 g/mol

LC-MS:
t_{ret} = 17,2 min
ES-MS [m/z (fragment, intensity)]: 366,1 ($M+H^+$, 10), 179,1 (dibenzofulvene, 90)

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ 7.70 (d, *J*=7.35 Hz, 2 H) 7.51 (d, *J*=7.35 Hz, 2 H) 7.39 - 7.21 (m, 4 H) 4.98 (br. s, 1 H) 4.52 (d, 6.45 Hz, 2 H) 4.16 (t, *J*=6.25 Hz, 1 H) 4.12 – 3.96 (m, 4 H) ppm

^{13}C NMR: (75 MHz, CHLOROFORM-d) δ 156.08 (COONH) 143.55 (C) 141.36 (C) 127.82 (CH) 127.09 (CH) 124.94 (CH) 120.07 (CH) 67.14 (CH_2) 64.71 (CH_2) 47.15 (CH) 36.32 (CH_2)

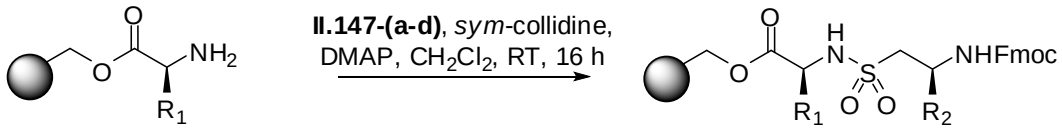
TLC: R_f = 0,20 (CH_2Cl_2 80/20)

11 SYNTHESIS OF 1,2,5-THIADIAZEPAN-4-ONE-1,1-DIOXIDES

11.1 COUPLING OF THE α-AMINO ACID ON WANG AND DEPROTECTION

GENERAL PROCEDURE: see section 2.1

11.2 COUPLING OF THE β-AMINOETHANESULFONYL CHLORIDE

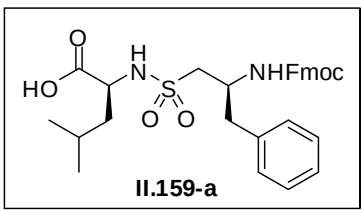


II.24 **II.159**

11.2.1 GENERAL PROCEDURE

The resin bound α-amino acid **II.24** (0.86 mmol, 1 eq) is suspended in 20 ml of CH_2Cl_2, followed by the consecutive addition of *sym*-collidine (0.677 ml, 5.13 mmol, 6 eq), the β-aminoethanesulfonyl chloride **II.147-(a-d)** (2.57 mmol, 3 eq) and DMAP (10.4 mg, 0.086, 0.1 eq). This reaction mixture is shaken for 16 h at room temperature, filtered off and washed with DMF, MeOH and CH_2Cl_2, readily delivering the sulfonamide **II.159**.

For compound **II.159-a**, with R_1 = iBu and R_2 = Bn LC-MS analysis after cleavage delivered the following result:



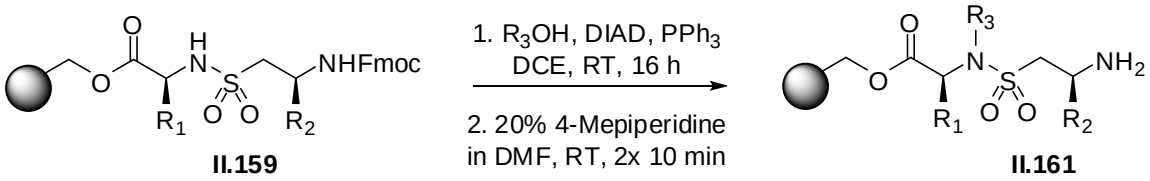
II.159-a

Formula: $C_{30}H_{34}N_2O_6S$

Molecular weight: 550,66 g/mol

LC-MS:
t_{ret} = 15,0 min
ES-MS [m/z (fragment, intensity)]: 549,1 ($M-H^+$, 15), 327,0 (M-Fmoc-H^+, 85)

11.3 INTRODUCTION OF THE R_3-GROUP USING THE MITSUNOBU-FUKUYAMA ALKYLATION AND FMOC DEPROTECTION

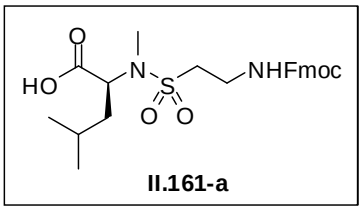


II.159 **II.161**

11.3.1 GENERAL PROCEDURE

Resin bound sulfonamide **II.159** (0.86 mmol, 1 eq) is suspended in 20 ml of DCE, followed by the subsequent addition of the alcohol (8.55 mmol, 10 eq), triphenylphosphine (1.12 g, 4.28 mmol, 5 eq) and DIAD (0.841 ml, 4.28 mmol, 5 eq). This reaction mixture is allowed to stir for 16h at room temperature, is filtered off and washed 3x with DMF, MeOH and CH_2Cl_2. The alkylated resin is then treated 2x with a 20% solution of 4-methylpiperidine in DMF, readily delivering the ring closing precursor **II.161**.

For compound **II.161-a**, with R_1 = iBu, R_2 = Bn and R_3 = Me, LC-MS analysis after cleavage delivered the following result:



II.161-a

Formula: $C_{24}H_{30}N_2O_6S$

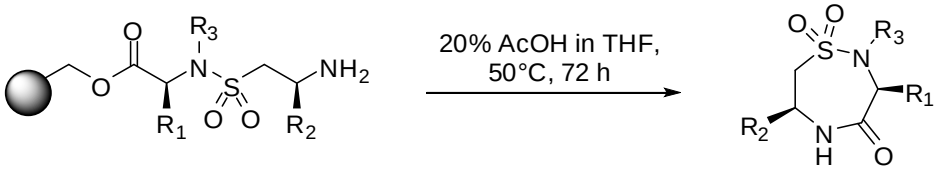
Molecular weight: 474,57 g/mol

LC-MS:

t_{ret} = 14,1 min

ES-MS [m/z (fragment, intensity)]: 473,1 ($M-H^+$, 10), 251,1 (M-Fmoc-H^+, 70), 947,3 (2M-H+, 20)

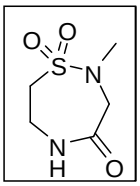
11.4 RING CLOSURE



II.161 **II.145**

Ring closing precursor **II.161** (0.261 mmol, 1 eq) is suspended in a 20% solution of acetic acid in THF and shaken for 72 h at 50°C. Subsequently, the resin is filtrated and washed with THF, the filtrate collected and evaporated under reduced pressure. The crude product is purified using column chromatography, readily delivering the desired 1,2,5-thiadiazepan-4-one-1,1-dioxides **II.145**.

11.4.1 2-METHYL-1,2,5-THIADIAZEPAN-4-ONE-1,1-DIOXIDE **II.145-A**



Formula: $C_5H_{10}N_2O_3S$

Molecular weight: 178,21 g/mol

Yield: 50%

LC-MS:
t_{ret} = 8,0 min
ES-MS [m/z (fragment, intensity)]: 177,0 ($M-H^+$, 100)

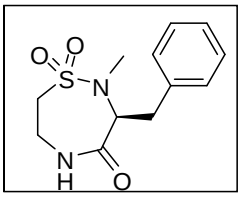
HR-MS (ESI): calculated for [$M-H^+$] = 177,0339, found 177,0263

^{1}H NMR (300 MHz, METHANOL-*d*$_4$) δ ppm 4.30 - 3.75 (br. s, 2H) 3.54 - 3.72 (m, 2 H) 3.21 - 3.30 (m, 2 H) 2.87 (s, 3 H)

^{13}C NMR: (75 MHz, METHANOL-*d*$_4$) δ 175.69 (C=O) 54.21 (CH_2) 50.61 (CH_2) 38.28 (CH_2) 35.42 (CH_3) ppm

TLC: R_f = 0,03 (CH_2Cl_2/EtOAc 80/20)

11.4.2 (3S)-BENZYL-2-METHYL-1,2,5-THIADIAZEPAN-4-ONE-1,1-DIOXIDE **II.145-B**



Formula: $C_{12}H_{16}N_2O_3S$

Molecular weight: 268,33 g/mol

Yield: 44%

LC-MS:
t_{ret} = 13,0 min
ES-MS [m/z (fragment, intensity)]: 267,0 ($M-H^+$, 100)
Purity: 95%

HR-MS (ESI): calculated for [$M-H^+$] = 269,0954, found 269,0953

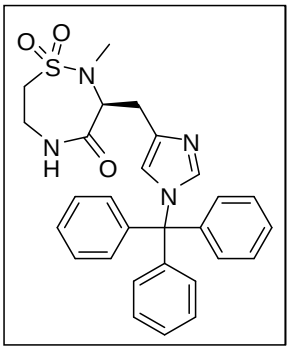
^{1}H NMR (300 MHz, METHANOL-*d*$_4$) δ ppm 7.25 - 7.34 (m, 4 H) 7.16 - 7.24 (m, 1 H) 4.82 (dd, *J*=9.0, 6.0 Hz, 1 H) 3.75 (ddd, *J*=16.2, 9.8, 3.2 Hz, 1 H) 3.42 - 3.53 (m, 1 H) 3.13 - 3.23 (m, 3 H) 2.97 (dd, *J*=14.7, 9.0 Hz, 1 H) 2.74 (s, 3 H)

^{13}C NMR: (75 MHz, METHANOL-*d*$_4$) δ 175.00 (C=O) 138.67 (C) 130.42 (CH) 129.29 (CH) 127.49 (CH) 59.76 (CH) 49.84 (CH_2) 37.73 (CH_2) 34.59 (CH_2) 30.61 (CH_3) ppm

TLC: R_f = 0,10 (CH_2Cl_2/EtOAc 80/20)

Optical rotation: $[\alpha]_D^{20}$ = -142° (c = 0.5, $CHCl_3$)

11.4.3 (3S)-2-METHYL-3-(1-TRITYLIMIDAZOL-4-YLMETHYL)-1,2,5-THIADIAZEPAN-4-ONE-1,1-DIOXIDE **II.145-C**



Formula: $C_{28}H_{28}N_4O_3S$

Molecular weight: 500,61 g/mol

Yield: 41%

LC-MS:
t_{ret} = 16,2 min
ES-MS [m/z (fragment, intensity)]: 499,1 ($M-H^+$, 100)
Purity: 97%

HR-MS (ESI): calculated for [$M+H^+$] = 501,1955, found 501,1937

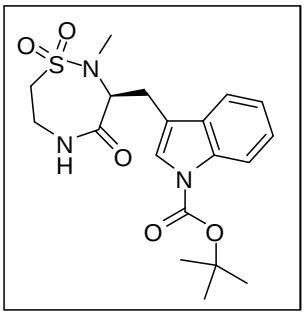
^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 7.28 - 7.39 (m, 10 H) 7.08 - 7.19 (m, 5 H) 6.90 (s, 1 H) 6.67 (s, 1 H) 4.79 (dd, *J*=9.7, 5.2 Hz, 1 H) 3.68 - 3.91 (m, 1 H) 3.34 - 3.50 (m, 1 H) 2.87 - 3.19 (m, 4 H) 2.68 (s, 3 H)

^{13}C NMR: (75 MHz, CHLOROFORM-*d*) δ 173.43 (C=O) 142.36 (C) 138.15 (CH) 136.14 (C) 129.82 (CH) 128.00 (CH) 127.93 (CH) 119.89 (CH) 75.23 (C) 57.37 (CH) 49.25 (CH_2) 37.09 (CH_2) 30.02 (CH_3) 26.61 (CH_2) ppm

TLC: R_f = 0.05 (CH_2Cl_2/ethyl acetate 80/20)

Optical rotation: $[\alpha]_D^{20}$ = -41° (c = 1 , $CHCl_3$)

11.4.4 (3S)-3-(N-*TERT*-BUTOXYCARBONYLINDOL-3-YLMETHYL)-2-METHYL-1,2,5-THIADIAZEPAN-4-ONE-1,1-DIOXIDE **II.145-D**



Formula: $C_{19}H_{25}N_3O_5S$

Molecular weight: 407,48 g/mol

Yield: 16%

LC-MS:
t_{ret} = 16,5 min
ES-MS [m/z (fragment, intensity)]: 406,1 ($M-H^+$, 100)
Purity: 100%

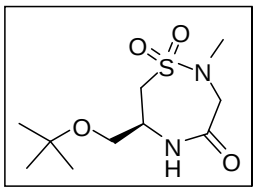
HR-MS (ESI): calculated for [$M-H^+$] = 406,1442, found 406,1310

^{1}H NMR (300 MHz, METHANOL-d_4) δ ppm 8.11 (d, *J*=7.9 Hz, 1 H) 7.71 (s, 1 H) 7.61 (dd, *J*=7.3, 1.7 Hz, 1 H) 7.31 (td, *J*=7.3, 1.3 Hz, 1 H) 7.25 (td, *J*=7.7, 1.5 Hz, 1 H) 4.97 (dd, *J*=8.7, 6.0 Hz, 1 H) 3.76 (ddd, *J*=16.2, 10.0, 2.8 Hz, 1 H) 3.43 - 3.55 (m, 1 H) 3.05 - 3.28 (m, 4 H) 2.77 (s, 3 H) 1.68 (s, 9 H)

^{13}C NMR: (75 MHz, METHANOL-*d*$_4$) δ 174.85 (C=O) 151.07 (NHCOO) 136.73 (C) 131.96 (C) 125.34 (CH) 123.62 (CH) 119.79 (CH) 117.22 (C) 116.03 (CH) 84.60 (C) 57.98 (CH) 49.95 (CH_2) 37.75 (CH_2) 30.55 (CH_3) 28.41 (CH_3) 24.18 (CH_2) ppm

TLC: R_f = 0,09 (CH_2Cl_2/EtOAc 80/20)

11.4.5 (6S)-6-(*TERT*-BUTOXYMETHYL)-2-METHYL-1,2,5-THIADIAZEPAN-4-ONE-1,1-DIOXIDE **II.145-E**



Formula: $C_{10}H_{20}N_2O_4S$

Molecular weight: 264,34 g/mol

Yield: 49%

LC-MS:

t_{ret} = 13,0 min

ES-MS [m/z (fragment, intensity)]: 427,1 ($M\text{-}H^+$, 100)

Purity: 80% (crude)

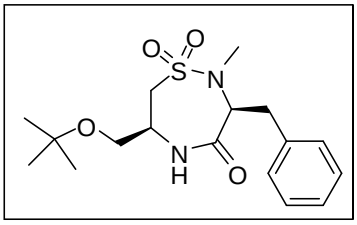
^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 6.12 (br. s., 1 H) 4.50 (d, *J*=15.8 Hz, 1 H) 4.00 - 4.12 (m, 1 H) 3.50 - 3.62 (m, 2 H) 3.44 (dd, *J*=9.2, 4.3 Hz, 1 H) 3.24 (dd, *J*=14.5, 10.2 Hz, 1 H) 3.12 (d, *J*=13.6 Hz, 1 H) 2.87 - 2.94 (m, 3 H) 1.12 - 1.23 (m, 9 H)

^{13}C NMR: (75 MHz, CHLOROFORM-*d*) δ 171.44 (C=O) 74.21 (C) 63.14 (CH_2) 53.70 (CH_2) 53.18 (CH_2) 49.16 (CH) 35.27 (CH_3) 27.27 (CH_3) ppm

TLC: R_f = 0,04 (CH_2Cl_2/aceton 80/20)

Optical rotation: $[\alpha]_D^{20}$ = -83° (c = 1.0, $CHCl_3$)

11.4.6 (3S,6S)-3-BENZYL-6-(*TERT*-BUTOXYMETHYL)-2-METHYL-1,2,5-THIADIAZEPAN-4-ONE-1,1-DIOXIDE **II.145-F**



Formula: $C_{17}H_{26}N_2O_4S$

Molecular weight: 354,46 g/mol

Yield: 42%

LC-MS:

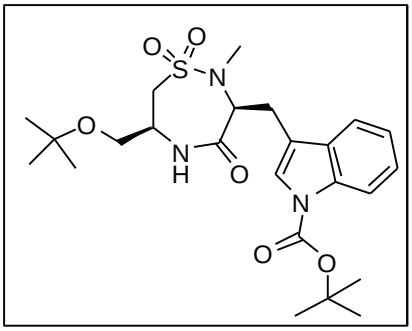
t_{ret} = 16,2 min

ES-MS [m/z (fragment, intensity)]: 353,1 ($M\text{-}H^+$, 100)

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 7.13 - 7.26 (m, 6 H) 6.04 (d, *J*=5.5 Hz, 1 H) 4.64 (t, *J*=7.2 Hz, 1 H) 3.89 - 4.03 (m, 1 H) 3.49 (dd, *J*=9.2, 3.6 Hz, 1 H) 3.36 (dd, *J*=9.0, 3.6 Hz, 1 H) 3.28 (dd, *J*=14.3, 7.3 Hz, 1 H) 3.10 (dd, *J*=14.5, 10.4 Hz, 1 H) 2.99 (dd, *J*=14.3, 1.1 Hz, 1 H) 2.90 (dd, *J*=14.3, 7.0 Hz, 1 H) 2.72 (s, 3 H) 1.12 (s, 9 H)

^{13}C NMR: (75 MHz, CHLOROFORM-*d*) δ 170.86 (C=O) 136.78 (C) 129.39 (CH) 128.49 (CH) 126.75 (CH) 74.16 (C) 63.20 (CH_2) 59.03 (CH) 52.49 (CH_2) 48.50 (CH) 33.96 (CH_2) 30.46 (CH_3) 27.27 (CH_3) ppm

11.4.7 (3S,6S)-3-(N-*TERT*-BUTOXYCARBONYLIMIDAZOL-3-YLMETHYL)-6-(*TERT*-BUTOXYMETHYL)-2-METHYL-1,2,5-THIADIAZEPAN-4-ONE-1,1-DIOXIDE **II.145-G**



Formula: $C_{24}H_{35}N_3O_6S$

Molecular weight: 493,62 g/mol

Yield: 20%

LC-MS:
t_{ret} = 19,0 min
ES-MS [m/z (fragment, intensity)]: 492,2 ($M-H^+$, 100)
Purity: 92%

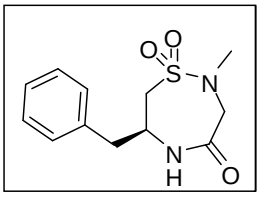
^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 8.14 (d, *J*=7.9 Hz, 1 H) 7.65 (s, 1 H) 7.60 (dd, *J*=7.2, 1.3 Hz, 1 H) 7.32 (td, *J*=7.3, 1.3 Hz, 1 H) 7.26 (td, *J*=7.3, 1.3 Hz, 1 H) 6.16 (d, *J*=5.8 Hz, 1 H) 4.86 (t, *J*=7.1 Hz, 1 H) 3.96 - 4.07 (m, 1 H) 3.55 (dd, *J*=9.2, 3.8 Hz, 1 H) 3.32 - 3.48 (m, 2 H) 3.20 (dd, *J*=14.3, 10.2 Hz, 1 H) 3.11 (s, 1 H) 3.06 (t, *J*=7.3 Hz, 1 H) 2.81 (s, 3 H) 1.65 (s, 9 H) 1.18 (s, 9 H)

^{13}C NMR: (75 MHz, CHLOROFORM-*d*) δ 170.73 (C=O) 149.61 (C) 135.36 (C) 130.31 (C) 124.49 (CH) 124.35 (CH) 122.57 (CH) 115.23 (CH) 115.14 (C) 83.41 (C) 74.13 (C) 63.15 (CH_2) 57.09 (CH) 52.60 (CH_2) 48.47 (CH) 30.39 (CH_3) 28.16 (CH_3) 27.24 (CH_3) 23.70 (CH_2) ppm

TLC: R_f = 0,45 (CH_2Cl_2/EtOAc 80/20)

Optical rotation: $[\alpha]_D^{20}$ = -307° (c = 0.125, $CHCl_3$)

11.4.8 (6S)-6-BENZYL-2-METHYL-1,2,5-THIADIAZEPAN-4-ONE-1,1-DIOXIDE **II.145-H**



Formula: $C_{12}H_{16}N_2O_3S$

Molecular weight: 268,33 g/mol

Yield: 92%

LC-MS:
t_{ret} = 13,0 min
ES-MS [m/z (fragment, intensity)]: 269,0 ($M+H^+$, 100)

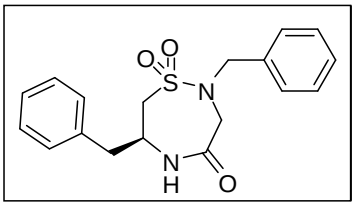
^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 7.28 - 7.42 (m, 3 H) 7.15 - 7.23 (m, 2 H) 5.73 (br. s., 1 H) 4.50 (d, *J*=16.0 Hz, 1 H) 4.13 - 4.27 (m, 1 H) 3.56 (dd, *J*=16.0, 2.1 Hz, 1 H) 3.24 (d, *J*=14.1 Hz, 1 H) 3.03 (dd, *J*=14.3, 10.4 Hz, 1 H) 2.94 (d, *J*=7.3 Hz, 2 H) 2.90 (s, 3 H)

^{13}C NMR: (75 MHz, CHLOROFORM-*d*) δ 171.69 (C=O) 134.33 (C) 129.45 (CH) 128.99 (CH) 128.09 (C) 54.32 (CH_2) 53.62 (CH_2) 49.78 (CH) 40.77 (CH_2) 35.26 (CH_3) ppm

TLC: R_f = 0,04 (CH_2Cl_2/aceton 80/20)

Optical rotation: $[\alpha]_D^{20}$ = -109° (c = 0.5, $CHCl_3$)

11.4.9 (6S)-2,6-DIBENZYL-1,2,5-THIADIAZEPAN-4-ONE-1,1-DIOXIDE **II.145-I**



Formula: $C_{18}H_{20}N_2O_3S$

Molecular weight: 344,43 g/mol

Yield: 47%

LC-MS:

t_{ret} = 5,8 min (method C)
ES-MS [m/z (fragment, intensity)]: 345,1 ($M+H^+$, 90), 689,1 ($2M+H^+$, 10)

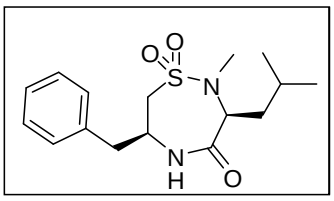
^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 7.28 - 7.43 (m, 8 H) 7.16 - 7.24 (m, 2 H) 5.70 (br. s., 1 H) 4.82 (dd, *J*=14.0, 1.4 Hz, 1 H) 4.32 (dd, *J*=16.4, 1.5 Hz, 1 H) 4.20 - 4.28 (m, 1 H) 3.81 (d, *J*=14.1 Hz, 1 H) 3.41 - 3.51 (m, 1 H) 3.37 (d, *J*=14.1 Hz, 1 H) 2.92 - 3.07 (m, 3 H)

^{13}C NMR: (75 MHz, CHLOROFORM-*d*) δ 171.92 (CONH) 134.33 (C) 134.11 (C) 129.46 (CH) 129.03 (CH) 129.01 (CH) 128.76 (CH) 128.34 (CH) 128.09 (CH) 56.32 (CH_2) 51.28 (CH_2) 49.84 (CH) 49.56 (CH_2) 40.87 ppm

TLC: R_f = 0,51 (CH_2Cl_2/ethyl acetate 80/20)

Optical rotation: $[\alpha]_D^{20}$ = -53° (c = 0.5, $CHCl_3$)

11.4.10 (3S,6S)-6-BENZYL-3-ISOBUTYL-2-METHYL-1,2,5-THIADIAZEPAN-4-ONE-1,1-DIOXIDE **II.145-J**



Formula: $C_{16}H_{24}N_2O_3S$

Molecular weight: 324,44 g/mol

Yield: 48%

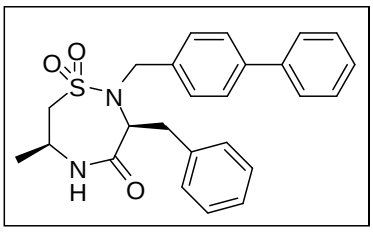
LC-MS:
t_{ret} = 16,0 min
ES-MS [m/z (fragment, intensity)]: 325,1 ($M+H^+$, 100)

^{1}H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 7.27 - 7.40 (m, 3 H) 7.19 (d, *J*=7.3 Hz, 2 H) 6.23 (d, *J*=31.2 Hz, 1 H) 4.46 (dd, *J*=10.2, 4.9 Hz, 1 H) 4.18 (dt, *J*=17.3, 7.3 Hz, 1 H) 3.17 (d, *J*=14.2 Hz, 1 H) 2.83 - 3.02 (m, 3 H) 2.67 (s, 3 H) 1.67 - 1.85 (m, 2 H) 1.42 - 1.52 (m, 1 H) 0.92 - 1.00 (m, 6 H)

^{13}C NMR: (125 MHz, CHLOROFORM-*d*) δ 172.56 (C=O) 134.69 (C) 129.24 (CH) 129.04 (CH) 127.82 (CH) 55.85 (CH) 53.32 (CH_2) 49.29 (CH) 40.62 (CH_2) 35.51 (CH_2) 29.91 (CH_3) 23.69 (CH) 23.28 (CH_3) 21.23 (CH_3) ppm

TLC: R_f = 0,75 (CH_2Cl_2/ethyl acetate 80/20)

11.4.11 (3S,6S)-3-BENZYL-2-(1,1'-BIPHENYL)-6-METHYL-1,2,5-THIADIAZEPAN-4-ONE-1,1-DIOXIDE **II.145-K**



Formula: $C_{25}H_{26}N_2O_3S$ (colorless oil)

Molecular weight: 434,55 g/mol

Yield: 17%

LC-MS:

t_{ret} = 13,8 min

ES-MS [m/z (fragment, intensity)]: 433,0 ($M-H^+$, 100)

Purity: 92%

HR-MS (ESI): calculated for [$M-H^+$] = 435,1737, found 435,1737

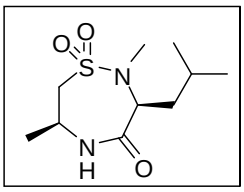
^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ 7.50 - 7.64 (m, 4 H) 7.41 - 7.50 (m, 4 H) 7.14 - 7.23 (m, 3 H) 7.03 - 7.12 (m, 2 H) 5.72 - 5.95 (m, 1 H) 4.91 (dd, *J*=8.3, 6.0 Hz, 1 H) 4.68 (d, *J*=16.0 Hz, 1 H) 4.10 - 4.22 (m, 1 H) 4.06 (d, *J*=16.0 Hz, 1 H) 3.14 - 3.29 (m, 2 H) 2.98 (dd, *J*=14.1, 10.5 Hz, 1 H) 2.74 (dd, *J*=14.3, 6.0 Hz, 1 H) 1.39 (d, *J*=6.6 Hz, 3 H) ppm

^{13}C NMR: (75 MHz, CHLOROFORM-*d*) δ 171.50 (C=O) 140.58 (C) 136.80 (C) 136.10 (C) 129.32 (CH) 128.75 (CH) 128.51 (CH) 128.23 (CH) 127.32 (CH) 127.13 (CH) 127.07 (CH) 126.47 (CH) 59.87 (CH) 56.98 (CH_2) 48.97 (CH_2) 44.53 (CH) 35.40 (CH_2) 21.22 (CH_3)ppm

TLC: R_f = 0,36 (CH_2Cl_2/ethyl acetate 80/20)

Optical rotation: $[\alpha]_D^{20}$ = -112° (c = 0.5, $CHCl_3$)

11.4.12 (3S,6S)-2,6-DIMETHYL-3-ISOBUTYL-1,2,5-THIADIAZEPAN-4-ONE-1,1-DIOXIDE **II.145-L**



Formula: $C_{10}H_{20}N_2O_3S$

Molecular weight: 248,34 g/mol

Yield: 70%

LC-MS:

t_{ret} = 13,4 min

ES-MS [m/z (fragment, intensity)]: 249,1 ($M+H^+$, 100)

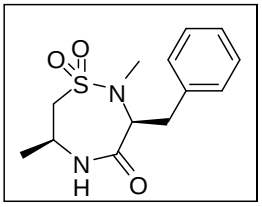
^{1}H NMR (500 MHz, CHLOROFORM-*d*) d ppm 5.83 (d, *J*=3.1 Hz, 1 H) 4.50 (dd, *J*=9.7, 5.1 Hz, 1 H) 4.05 - 4.17 (m, 1 H) 3.12 (d, *J*=14.0 Hz, 1 H) 2.98 (dd, *J*=14.2, 10.7 Hz, 1 H) 2.64 - 2.76 (m, 3 H) 1.70 - 1.83 (m, 2 H) 1.47 - 1.57 (m, 1 H) 1.40 (d, *J*=6.7 Hz, 3 H) 0.98 (t, *J*=6.1 Hz, 6 H)

^{13}C NMR: (75 MHz, CHLOROFORM-*d*) δ 172.43 (C=O) 55.88 (CH) 55.44 (CH_2) 44.43 (CH) 35.65 (CH_2) 29.98 (CH_3) 23.77 (CH) 23.25 (CH_3) 21.31 (CH_3) 21.24 (CH_3)

TLC: R_f = 0,02 (CH_2Cl_2/EtOAc 80/20)

Optical rotation: $[\alpha]_D^{20}$ = -102° (c = 0.925, $CHCl_3$)

11.4.13 (3S,6S)-3-BENZYL-2,6-DIMETHYL-1,2,5-THIADIAZEPAN-4-ONE-1,1-DIOXIDE **II.145-M**



Formula: $C_{13}H_{18}N_2O_3S$

Molecular weight: 282,36 g/mol

Yield: 60%

LC-MS:

t_{ret} = 13,5 min

ES-MS [m/z (fragment, intensity)]: 283,1 ($M+H^+$, 100)

HR-MS (ESI): calculated for [$M+H^+$] = 283,1110, found 283,1110

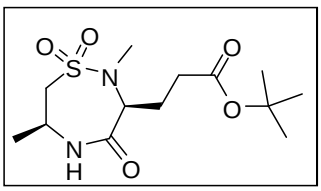
^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 7.27 - 7.34 (m, 4 H) 7.17 - 7.24 (m, 1 H) 5.99 (br. s., 1 H) 4.72 (t, *J*=7.2 Hz, 1 H) 3.94 - 4.12 (m, 1 H) 3.33 (dd, *J*=14.3, 7.5 Hz, 1 H) 3.09 (d, *J*=13.8 Hz, 1 H) 2.89 - 3.03 (m, 2 H) 2.78 (s, 3 H) 1.36 (d, *J*=6.8 Hz, 3 H)

^{13}C NMR: (75 MHz, CHLOROFORM-*d*) δ 171.35 (C=O) 136.70 (C) 129.37 (CH) 128.47 (CH) 126.75 (CH) 58.96 (CH) 55.44 (CH_2) 44.40 (CH) 34.02 (CH_2) 30.45 (CH_3) 21.12 (CH_3) ppm

TLC: R_f = 0,12 (CH_2Cl_2/EtOAc 80/20)

Optical rotation: $[\alpha]_D^{20}$ = -105° (c = 0.5, $CHCl_3$)

11.4.14 (3S,6S)-3-(*TERT*-BUTYLPROPIONYL)-2,6-DIMETHYL-1,2,5-THIADIAZEPAN-4-ONE-1,1-DIOXIDE **II.145-N**



Formula: $C_{13}H_{24}N_2O_5S$

Molecular weight: 320,41 g/mol

Yield: 68%

LC-MS:

t_{ret} = 13,9 min

ES-MS [m/z (fragment, intensity)]: 265,0 ($M-tBu+2H^+$, 100)

Purity: 95%

HR-MS (ESI): calculated for [$M-H^+$] = 319,1333 , found 319,1327

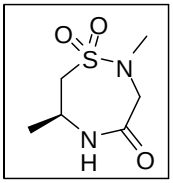
^{1}H NMR (300 MHz, Solvent) δ 6.00 – 5.77 (m, 1 H) 4.47 (s, 1 H) 4.05 – 3.92 (m, 1 H) 3.09 – 2.83 (m, 2 H) 2.62 (s, 3 H) 2.36 - 2.22 (m, 2 H) 2.05 – 1.89 (m, 2 H) 1.39 (s, 9 H) 1.32 (d, *J*=6.6 Hz, 3 H) ppm

^{13}C NMR: (75 MHz, CHLOROFORM-*d*) δ 172.02 (C=O) 171.89 (C=O) 80.69 (C) 57.04 (CH) 55.38 (CH_2) 44.44 (CH) 30.57 (CH_2) 30.06 (CH_3) 28.05 (CH_3) 22.02 (CH_2) 21.16 (CH_3) ppm

TLC: R_f = 0,04 (CH_2Cl_2/EtOAc 80/20)

Optical rotation: $[\alpha]_D^{20}$ = -75° (c = 1.0, $CHCl_3$)

11.4.15 (6S)-2,6-DIMETHYL-1,2,5-THIADIAZEPAN-4-ONE-1,1-DIOXIDE **II.145-O**



Formula: $C_6H_{12}N_2O_3S$

Molecular weight: 192,24 g/mol

Yield: 48%

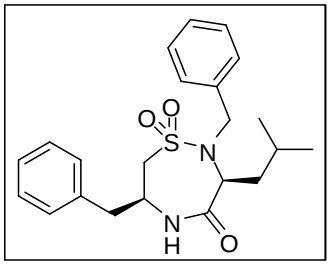
LC-MS:
t_{ret} = 10,8 min
ES-MS [m/z (fragment, intensity)]: 191,0 ($M-H^+$, 100)

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 5.68 (br. s., 1 H) 4.53 (d, *J*=16.0 Hz, 1 H) 4.03 - 4.16 (m, 3 H) 3.57 (dd, *J*=16.0, 1.9 Hz, 1 H) 2.96 - 3.15 (m, 2 H) 2.92 (s, 3 H) 1.41 (d, *J*=6.8 Hz, 3 H)

^{13}C NMR: (75 MHz, CHLOROFORM-*d*) δ 171.72 (C=O) 56.26 (CH_2) 53.60 (CH_2) 45.08 (CH) 35.24 (CH_3) 21.32 (CH_3) ppm

TLC: R_f = 0,04 (CH_2Cl_2/aceton 80/20)

11.4.16 (3S,6S)-2,6-DIBENZYL-3-ISOBUTYL-1,2,5-THIADIAZEPAN-4-ONE-1,1-DIOXIDE **II.145-P**



Formula: $C_{22}H_{28}N_2O_3S$

Molecular weight: 400,53 g/mol

Yield: 77%

LC-MS:
t_{ret} = 17,9 min
ES-MS [m/z (fragment, intensity)]: 399,1 ($M-H^+$, 100)

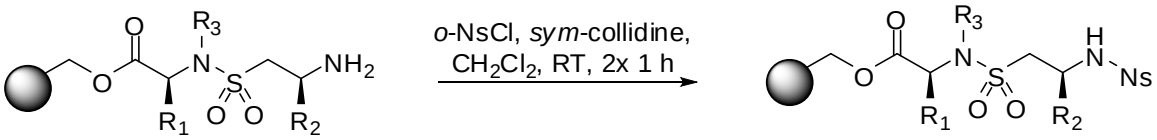
^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 7.27 - 7.45 (m, 8 H) 7.17 - 7.24 (m, 2 H) 5.72 (br. s., 1 H) 4.48 - 4.64 (m, 2 H) 4.18 - 4.33 (m, 1 H) 3.83 (d, *J*=15.8 Hz, 1 H) 3.31 (d, *J*=13.9 Hz, 1 H) 2.83 - 3.05 (m, 3 H) 1.47 - 1.64 (m, 2 H) 1.33 - 1.47 (m, 1 H) 1.17 - 1.33 (m, 1 H) 0.83 (d, *J*=6.4 Hz, 3 H) 0.44 (d, *J*=6.4 Hz, 3 H)

^{13}C NMR: (125 MHz, CHLOROFORM-*d*) δ 172.96 (C=O) 137.13 (C) 134.40 (C) 129.40 (CH) 129.10 (CH) 128.35 (CH) 128.31 (CH) 128.01 (CH) 127.66 (CH) 57.34 (CH) 54.93 (CH_2) 49.32 (CH) 49.20 (CH_2) 40.90 (CH_2) 36.71 (CH_2) 23.27 (CH) 22.58 (CH_3) 21.10 (CH_3) ppm

TLC: R_f = 0,03 (hexane/EtOac 80/20)

11.5 SYNTHESIS OF N_5-ALKYLATED 1,2,5-THIADIAZEPAN-4-ONE-1,1-DIOXIDES

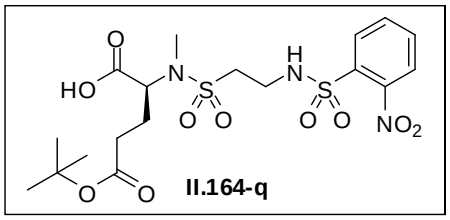
11.5.1 NOSYL PROTECTION



II.161 **II.164**

The primary amine of compound **II.161** (0.60 mmol, 1 eq) is suspended in 6 ml of CH_2Cl_2, followed by the addition of *sym*-collidine (0.395 ml, 3.00 mmol, 2.5 eq) and *ortho*-nosyl chloride (332 mg, 1.50 mmol, 2.5 eq). After 1 h shaking at room temperature, the resin is filtered off and washed 3x with DMF, MeOH and CH_2Cl_2. This procedure is repeated for a second time, readily yielding the nosylated product **II.164**.

For compound **II.164**, with R_1 = $(CH_2)_2COOtBu$, R_2 = H and R_3 = Me, LC-MS analysis after cleavage delivered the following result:



II.164-q

Formula: $C_{18}H_{27}N_3O_{10}S_2$

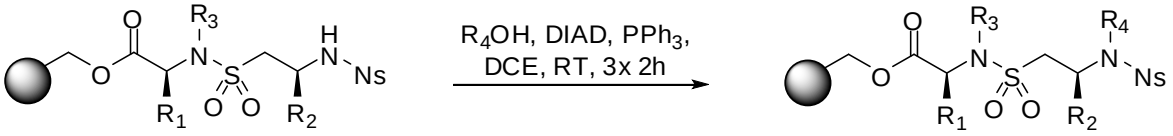
Molecular weight: 509,11 g/mol

LC-MS:

t_{ret} = 9,5 min (Method A)

ES-MS [m/z (fragment, intensity)]: 452,0 (M-*t*Bu-H^+, 100)

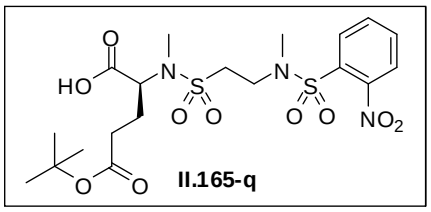
11.5.2 INTRODUCTION OF THE R_4-GROUP USING THE MITSUNOBU-FUKUYAMA ALKYLATION



II.164 **II.165**

The nosylated product **II.164** (0.261 mmol, 1 eq) is suspended in 6 ml of CH_2Cl_2, followed by consecutive addition of the alcohol (2.61 mmol, 10 eq), triphenylphosphine (343 mg, 1.31 mmol, 5 eq) and DIAD (0.257 ml, 1.31 mmol, 5 eq). After this suspension is shaken for 2 h at room temperature, the resin is filtered off and washed with DMF, MeOH and CH_2Cl_2. These reaction conditions are applied two more times on this resin, readily yielding the desired alkylated compound **II.165**.

For compound **II.165**, with R_1 = $(CH_2)_2COOtBu$, R_2 = H, R_3 = Me and R_4 = Me, LC-MS analysis after cleavage delivered the following result:



II.165-q

Formula: $C_{18}H_{27}N_3O_{10}S_2$

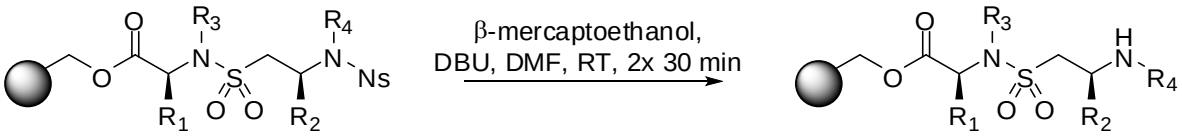
Molecular weight: 523,58 g/mol

LC-MS:

t_{ret} = 9,7 min (Method A)

ES-MS [m/z (fragment, intensity)]: 466,0 (M-*t*Bu-H^+, 100)

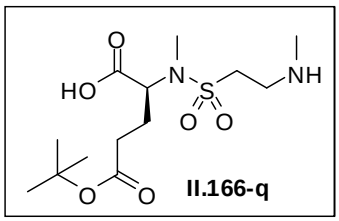
11.5.3 NOSYL DEPROTECTION



II.165 **II.166**

Resin **II.165** (0.261 mmol, 1 eq) is suspended in 4 ml DMF, followed by the addition of DBU (0.195 ml, 1.31. mmol, 5 eq) and β-mercaptoethanol (0.046 ml, 0.65 mmol, 2.5 eq). This suspension is shaken at room temperature for 30 min, then the resin is filtered off and washed 3x with DMF, MeOH and CH_2Cl_2. This procedure is performed a second time on this resin, readily yielding the deprotected amine **II.166**.

For compound **II.166**, with R_1 = $(CH_2)_2COOtBu$, R_2 = H, R_3 = Me and R_4 = Me, LC-MS analysis after cleavage delivered the following result:



II.166-q

Formula: $C_{13}H_{26}N_2O_6S$

Molecular weight: 338,42 g/mol

LC-MS:

t_{ret} = 2,9 min (Method A)

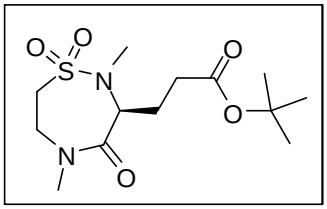
ES-MS [m/z (fragment, intensity)]: 281,1 (M-*t*Bu-H^+, 100)

11.6 RING CLOSURE OF N_5 ALKYLATED THIADIAZEPANONES

Procedure: see ring closure of non-N_5 alkylated thiadiazepanones

12 SYNTHESIS OF THE 1,2,5-THIADIAZEPAN-4-ONE-1,1-DIOXIDES

12.1.1 (3S)-3-(*TERT*-BUTYLPROPIONYL)-2,5-DIMETHYL-1,2,5-THIADIAZEPAN-4-ONE-1,1-DIOXIDE **II.145-Q**



Formula: $C_{13}H_{24}N_2O_5S$

Molecular weight: 320,41 g/mol

Yield: 38%

LC-MS:

t_{ret} = 13,8 min

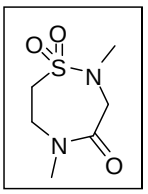
ES-MS [m/z (fragment, intensity)]: 265,1 (M-tBu+2H$^+$, 100)

^{1}H NMR: (300 MHz, CHLOROFORM-*d*) δ ppm 4.50 (t, *J*=7.7 Hz, 1 H) 4.05 (ddd, *J*=16.8, 10.7, 1.7 Hz, 1 H) 3.37 (ddd, *J*=16.7, 5.2, 2.2 Hz, 1 H) 2.93 - 3.14 (m, 5 H) 2.55 (s, 3 H) 2.25 - 2.35 (m, 2 H) 1.92 - 2.04 (m, 2 H) 1.38 (s, 9 H)

^{13}C NMR: (75 MHz, CHLOROFORM-*d*) δ 172.10 (C=O) 170.72 (C=O) 80.62 (C) 57.17 (CH) 47.42 (CH_2) 45.51 (CH_2) 36.37 (CH_3) 30.76 (CH_2) 30.16 (CH_3) 28.07 (CH_3) 22.83 (CH_2) ppm

TLC: R_f = 0,06 (CH_2Cl_2/EtOAc 80/20)

12.1.2 2,5-DIMETHYL-1,2,5-THIADIAZEPAN-4-ONE-1,1-DIOXIDE **II.145-R**



Formula: $C_6H_{12}N_2O_3S$

Molecular weight: 192,24 g/mol

Yield: 22%

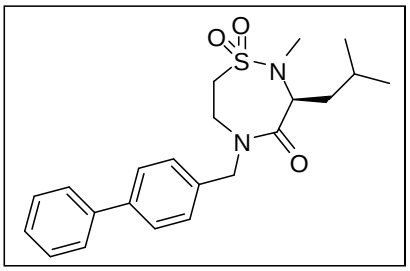
LC-MS:

t_{ret} = 9,2 min

ES-MS [m/z (fragment, intensity)]: 193,1 (M-H$^+$, 100)

^{1}H NMR: (300 MHz, CHLOROFORM-*d*) δ 4.76 - 3.22 (br. m, 4 H) 3.21 - 3.11 (m, 2 H) 3.07 (s, 3 H) 2.84 (s, 3 H) ppm

12.1.3 (3S)-5-(4-PHENYLBENZYL)-3-ISOBUTYL-2-METHYL-1,2,5-THIADIAZEPAN-4-ONE-1,1-DIOXIDE **II.145-S**



Formula: $C_{22}H_{28}N_2O_3S$

Molecular weight: 400,53 g/mol

Yield: 9%

LC-MS:

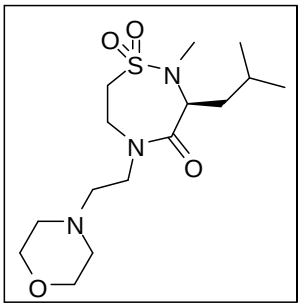
t_{ret} = 18,5 min

ES-MS [m/z (fragment, intensity)]: 401,1 ($M+H^+$, 100)

^{1}H NMR: (300 MHz, CHLOROFORM-*d*) δ ppm 7.54 - 7.63 (m, 5 H) 7.41 - 7.50 (m, 2 H) 7.31 - 7.41 (m, 3 H) 4.88 (d, *J*=14.3 Hz, 1 H) 4.48 - 4.60 (m, 2 H) 4.05 (dd, *J*=16.7, 11.8 Hz, 1 H) 3.55 (ddd, *J*=16.8, 5.7, 1.7 Hz, 1 H) 3.02 (dd, *J*=14.4, 5.0 Hz, 1 H) 2.69 - 2.78 (m, 1 H) 2.66 (s, 3 H) 1.82 - 1.96 (m, 1 H) 1.60 - 1.67 (m, 1 H) 1.16 - 1.32 (m, 2 H) 1.00 (dd, *J*=6.5, 2.7 Hz, 7 H)

^{13}C NMR: (75 MHz, CHLOROFORM-*d*) δ 171.33 (C=O) 141.27 (C) 140.24 (C) 135.53 (C) 128.97 (CH) 128.86 (CH) 127.76 (C) 127.61 (CH) 127.05 (CH) 56.12 (CH) 51.70 (CH_2) 48.10 (CH_2) 43.17 (CH_2) 36.65 (CH_2) 30.05 (CH_3) 23.91 (CH) 23.32 (CH_3) 21.46 (CH_3) ppm

12.1.4 (3S)-3-ISOBUTYL-2-METHYL-5-(N-MORPHOLINOETHYL)-1,2,5-THIADIAZEPAN-4-ONE-1,1-DIOXIDE **II.145-T**



Formula: $C_{15}H_{29}N_3O_4S$

Molecular weight: 347,47 g/mol

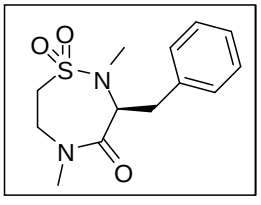
Yield: 18%

LC-MS:

t_{ret} = 13,8 min

ES-MS [m/z (fragment, intensity)]: 348,2 ($M+H^+$, 100)

12.1.5 (3S)-3-BENZYL-2,5-DIMETHYL-1,2,5-THIADIAZEPAN-4-ONE-1,1-DIOXIDE **II.145-U**



Formula: $C_{13}H_{18}N_2O_3S$

Molecular weight: 282,36 g/mol

Yield: 30%

LC-MS:

t_{ret} = 13,8 min

ES-MS [m/z (fragment, intensity)]: 283,1 ($M+H^+$, 100)

HR-MS (ESI): calculated for [$M+H^+$] = 283,1111, found 283,1112

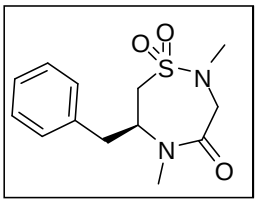
^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 7.28 - 7.32 (m, 4 H) 7.18 - 7.25 (m, 1 H) 4.76 (t, *J*=7.2 Hz, 1 H) 4.11 (ddd, *J*=16.8, 11.2, 1.2 Hz, 1 H) 3.42 (ddd, *J*=16.8, 5.5, 1.9 Hz, 1 H) 3.35 (dd, *J*=14.1, 7.3 Hz, 1 H) 3.02 - 3.18 (m, 5 H) 2.92 - 3.02 (m, 1 H) 2.72 (s, 3 H)

^{13}C NMR: (75 MHz, CHLOROFORM-*d*) δ 170.23 (C=O) 136.94 (C) 129.44 (CH) 128.45 (CH) 126.69 (CH) 59.15 (CH) 47.39 (CH_2) 45.48 (CH_2) 36.48 (CH_3) 34.80 (CH_2) 30.53 (CH_3) ppm

TLC: R_f = 0,19 (CH_2Cl_2/EtOAc 80/20)

Optical rotation: $[\alpha]_D^{20}$ = -155° (c = 0.25, $CHCl_3$)

12.1.6 (6S)-6-BENZYL-2,5-DIMETHYL-1,2,5-THIADIAZEPAN-4-ONE-1,1-DIOXIDE **II.145-V**



Formula: $C_{13}H_{18}N_2O_3S$

Molecular weight: 282,36 g/mol

Yield: 41%

LC-MS:

t_{ret} = 13,7 min

ES-MS [m/z (fragment, intensity)]: 283,1 ($M+H^+$, 100)

HR-MS (ESI): calculated for [$M+H^+$] = 283,1111 , found 283,1119

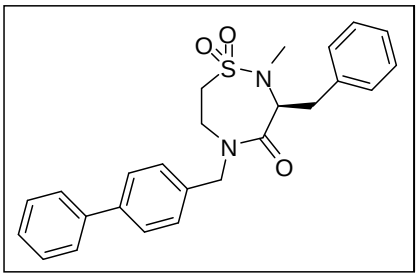
^{1}H NMR: (300 MHz, CHLOROFORM-*d*) δ ppm 7.27 - 7.40 (m, 3 H) 7.18 - 7.25 (m, 2 H) 3.86 - 4.09 (m, 1 H) 3.18 - 3.31 (m, 1 H) 3.00 - 3.18 (m, 3 H) 2.96 (s, 16 H) 2.83 (s, 3 H)

^{13}C NMR: (75 MHz, CHLOROFORM-*d*) δ 170.77 (C=O) 129.19 (CH) 128.76 (CH) 127.61 (CH) 54.31 (CH_2) 50.62 (CH_2) 38.45 (CH_2) 35.34 (CH_3) ppm (one CH_3 could not be detected)

TLC: R_f = 0,19 (CH_2Cl_2/EtOAc 80/20)

Optical rotation: $[\alpha]_D^{20}$ = -73° (c = 0.5, $CHCl_3$)

12.1.7 (3S)-3-BENZYL-5-(4-PHENYLBENZYL)-2-METHYL-1,2,5-THIADIAZEPAN-4-ONE-1,1-DIOXIDE **II.145-W**



Formula: $C_{25}H_{26}N_2O_3S$

Molecular weight: 434,55 g/mol

Yield: 12%

LC-MS:

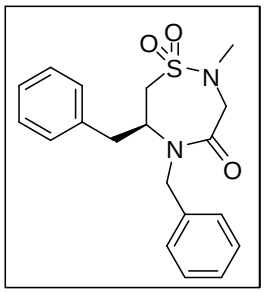
t_{ret} = 18,1 min

ES-MS [m/z (fragment, intensity)]: 435,1 ($M+H^+$, 100)

^{1}H NMR: (300 MHz, DMSO-d_6) δ ppm 8.45 (br. s., 1 H) 7.81 (d, *J*=8.1 Hz, 1 H) 7.26 - 7.36 (m, 4 H) 7.19 - 7.24 (m, 1 H) 7.16 (d, *J*=8.1 Hz, 1 H) 7.04 (br. s., 1 H) 4.65 (dd, *J*=8.7, 5.7 Hz, 1 H) 3.60 (dd, *J*=14.5, 5.7 Hz, 1 H) 3.10 (dd, *J*=14.5, 9.0 Hz, 1 H) 2.68 (s, 3 H) 2.50 (br. s., 3 H) 2.31 (s, 3 H)

TLC: R_f = 0,04 (CH_2Cl_2/aceton 80/20)

12.1.8 (6S)-5,6-DIBENZYL-2-METHYL-1,2,5-THIADIAZEPAN-4-ONE-1,1-DIOXIDE **II.145-X**



Formula: $C_{19}H_{22}N_2O_3S$

Molecular weight: 358,45 g/mol

Yield: 10%

LC-MS:
t_{ret} = 16,6 min
ES-MS [m/z (fragment, intensity)]: 359,1 ($M+H^+$, 100)

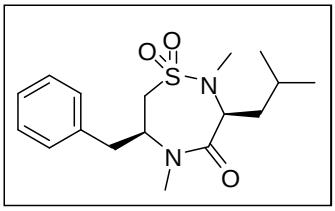
HR-MS (ESI): calculated for [$M+H^+$] = 359,1424 found 359,1428

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 7.42 - 7.28 (m, 7 H) 7.19 - 7.10 (m, 3 H) 5.13 - 4.81 (m, 1 H) 4.80 - 4.36 (m, 1 H) 4.34 - 3.72 (m, 3 H) 3.47 - 3.25 (m, 1 H) 3.18 - 2.97 (m, 2 H) 2.93 (s, 3 H) 2.87 (dd, *J*=14.79, 3.10 Hz, 1 H)

^{13}C NMR: (75 MHz, CHLOROFORM-*d*) δ 171.62 (C=O) 145.32 (C) 136.61 (C) 132.80 (C) 129.32 (CH) 128.57 (CH) 128.21 (C) 126.87 (CH) 124.57 (CH) 121.14 (CH) 62.16 (CH_2) 62.20 (CH_2) 61.92 (CH) 53.62 (CH_2) 35.74 (CH_2) 32.40 (CH_3) ppm

TLC: R_f = 0,49 (CH_2Cl_2/EtOAc 80/20)

12.1.9 (3S,6S)-6-BENZYL-2,5-DIMETHYL-3-ISOBUTYL-1,2,5-THIADIAZEPAN-4-ONE-1,1-DIOXIDE **II.145-Y**



Formula: $C_{17}H_{26}N_2O_3S$

Molecular weight: 338,46 g/mol

Yield: 3%

LC-MS:

t_{ret} = 13,8 min
ES-MS [m/z (fragment, intensity)]: 339,1 ($M+H^+$, 100)

HR-MS (ESI): calculated for [$M+H^+$] = 339,1714, found 339,1743

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 7.28 - 7.43 (m, 3 H) 7.17 - 7.25 (m, 2 H) 4.72 (dd, J=9.32, 5.37 Hz, 1 H) 4.54 - 4.67 (m, 1 H) 3.20 - 3.33 (m, 1 H) 2.99 - 3.03 (m, 3 H) 2.59 (s, 3 H) 1.68 - 1.91 (m, 2 H) 1.47 - 1.65 (m, 4 H) 0.94 - 1.06 (m, 6 H)7.81 (d, *J*=8.1 Hz, 1 H) 7.26 - 7.36 (m, 4 H)

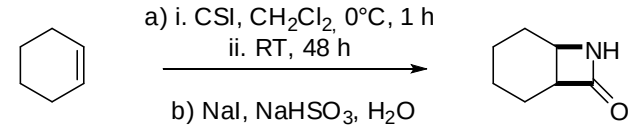
^{13}C NMR: (75 MHz, CHLOROFORM-*d*) δ 171.71 (C=O) 135.37 (C) 129.25 (CH) 128.62 (CH) 127.63 (CH) 56.26 (CH) 53.41 (CH) 49.85 (CH_2) 39.03 (CH_2) 36.47 (CH_2) 30.10 (CH_3) 28.56 (CH_3) 24.03 (CH_3) 23.25 (CH) 21.59 (CH_3) ppm

TLC: R_f = 0,37 (CH_2Cl_2/EtOAc 80/20)

13 SYNTHESIS OF 3,4-DIHYDRO-2*H*-1,2,6-THIADIAZOCIN-5(6*H*)-ONE-1,1-DIOXIDES

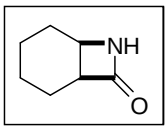
13.1 SYNTHESIS OF ALICYCLIC β-AMINO ACIDS **II.170**

13.1.1 (±)-*CIS*-7-AZABICYCLO[4.2.0]OCTAN-8-ON **II.173-A**



II.171-a **II.173-a**

Cyclohexene **II.171-a** (25.0 ml, 246 mmol, 1 eq) is brought into a flask and stirred at 0°C. Subsequently, chlorosulfonyl isocyanate (20.4 ml, 234 mmol, 0.95 eq) is added dropwise to the cyclohexene during a period of 25 min. This reaction is allowed to stir further at 0°C for 1 h and 48 h at room temperature and turns from a yellow to brown solution. The reaction mixture is then poured into an ice-cold solution of NaI (0.552 g, 3.70 mmol, 0.015 eq) and $NaHSO_3$ (1.68 g, 16.1 mmol, 0.065 eq) in 130 ml of water. The pH of the resulting solution is then brought to 7 by dropwise adding a 12 M solution of NaOH, resulting in the visual formation of gas. Then, the resulting suspension is extracted 5x with 300 ml of EtOAc, the organic phases collected and washed 3x with 800 ml of brine, dried on $MgSO_4$ and evaporated under reduced pressure. After purification using column chromatography (eluens: hexane/ethyl acetate 50/50), the pure β-lactam **II.173-a** is obtained as a yellowish solid in 55% yield.



Formula: $C_7H_{11}NO$

Molecular weight: 125,17 g/mol

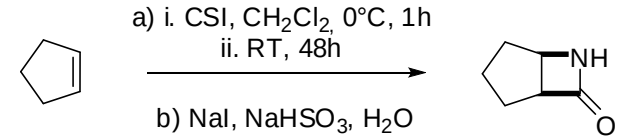
Yield: 55%

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 5.80 (s, 1 H) 3.82 (m, 1 H) 3.20 (m, 1 H) 1.93-1.79 (m, 1 H) 1.79-1.55 (m, 5 H) 1.54-1.36 (m, 2 H)

^{13}C NMR: (75 MHz, CHLOROFORM-*d*) δ 172.25 (C=O) 47.68 (CH) 46.81 (CH) 25.69 (CH_2) 19.88 (CH_2) 18.98 (CH_2) 16.87 (CH_2) ppm

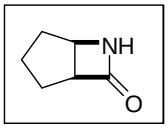
TLC: R_f = 0,25 (pentane/EtOAc 30/70)

13.1.2 (±)-*CIS*-6-AZABICYCLO[3.2.0]HEPTAN-7-ON **II.173-B**



II.171-b **II.173-b**

Cyclopentene **II.171-b** (25.0 ml, 246 mmol, 1 eq) is brought into a flask and stirred at 0°C. Subsequently, chlorosulfonyl isocyanate (18.7 ml, 215 mmol, 0.95 eq) is added dropwise to the cyclopentene during a period of 25 min. This reaction is allowed to stir at 0°C for 8 h and further at room temperature overnight. The reaction mixture is then poured into an ice-cold solution of NaI (0.508 g, 3.39 mmol, 0.015 eq) and $NaHSO_3$ (1.55 g, 14.9 mmol, 0.065 eq) in 120 ml of water. The pH of the resulting solution is then brought to 7 by dropwise adding a 12 M solution of NaOH, resulting in the visual formation of gas. Then, the resulting suspension is extracted 5x with 300 ml of EtOAc, the organic phases collected and washed 3x with 800 ml of brine, dried on $MgSO_4$ and evaporated under reduced pressure. After purification using column chromatography (eluens: hexane/ethyl acetate 50/50), the pure β-lactam **II.173-b** is obtained as a yellowish solid in 72% yield.



Formula: C_6H_9NO

Molecular weight: 111,14 g/mol

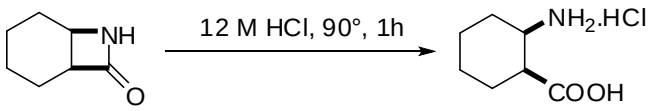
Yield: 72%

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 5.77 (app. s, 1 H) 3.99 (m, 1 H) 3.44 (m, 1 H) 1.97 (m, 1 H) 1.85-1.63 (m, 3 H) 1.45-1.21 (m, 2 H)

^{13}C NMR: (75 MHz, CHLOROFORM-*d*) δ 170.71 (C=O) 56.02 (CH) 53.94 (CH) 30.05 (CH_2) 25.23 (CH_2) 22.42 (CH_2) ppm

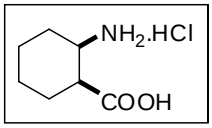
TLC: R_f = 0,25 (pentane/EtOAc 30/70)

13.1.3 (±)-*CIS*-2-AMINOCYCLOHEXANECARBOXYLIC ACID HYDROCHLORIDE **II.174-A**



II.173-a **II.174-a**

To the lactam **II.173-a** (8.38 g, 66.8 mmol, 1 eq) is added 90 ml of concentrated HCl and this suspension is stirred for 1 h at 90°C. The resulting brown solution is subsequently evaporated under reduced pressure, yielding the crude β-amino acid hydrochloric acid. This salt is recrystallized by dissolving it in ethanol under reflux, followed by the addition of ether until a white precipitate is formed. This white precipitate is filtered off and washed with ether, delivering the desired hydrochloric acid salt. The filtrate is again evaporated under reduced pressure and submitted to the same recrystallization conditions. This step is repeated until no more precipitate is formed. Finally, the pure amino acid salt **II.174-a** is obtained as a white powder in 93% yield.



Formula: $C_7H_{14}ClNO_2$

Molecular weight: 179,64 g/mol

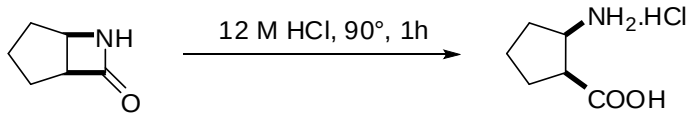
Yield: 93%

LC-MS:
t_{ret} = 7,8 min
ES-MS [m/z (fragment, intensity)]: 144,1 ($M+H^+$, 100)

^{1}H NMR (300 MHz, D_2O) δ ppm 3.49 (m, 1 H) 2.92 (m, 1 H) 1.95 (m, 1 H) 1.76 (m, 2 H) 1.71-1.55 (m, 2 H) 1.52-1.25 (m, 3 H)

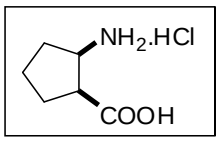
^{13}C NMR: (75 MHz, D_2O) δ 176.71 (C=O) 49.74 (CH) 41.97 (CH) 27.10 (CH_2) 25.84 (CH_2) 22.12 (CH_2) 22.03 (CH_2) ppm

13.1.4 (±)-*CIS*-2-AMINOCYCLOPENTANECARBOXYLIC ACID HYDROCHLORIC ACID **II.174-B**



II.173-b **II.174-b**

To the lactam **II.173-b** (17.1 g, 154 mmol, 1 eq) is added concentrated 120 ml HCl and this suspension is stirred for 1 h at 90°C. The resulting brown solution is subsequently evaporated under reduced pressure, yielding the crude β-amino acid hydrochloric acid. This salt is recrystallized by dissolving it in ethanol under reflux, followed by the addition of ether until a white precipitate is formed. This white precipitate is filtered off and washed with ether, delivering the desired hydrochloric acid salt. The filtrate is again evaporated under reduced pressure and submitted to the same recrystallization conditions. This step is repeated until no more precipitate is formed. Finally, the pure amino acid salt **II.174-b** is obtained as a white powder in 64% yield.



Formula: $C_6H_{12}ClNO_2$

Molecular weight: 165,62 g/mol

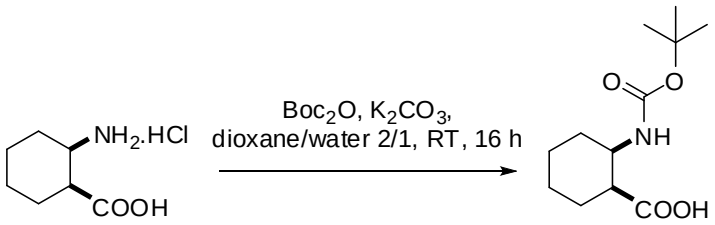
Yield: 64%

LC-MS:
t_{ret} = 4,3 min
ES-MS [m/z (fragment, intensity)]: 130,1 ($M+H^+$, 100)

^{1}H NMR (300 MHz, D_2O) δ ppm 3.83 (m, 1 H) 3.12 (m, 1 H) 2.22-2.03 (m, 2 H) 2.01-1.62 (m, 4 H)

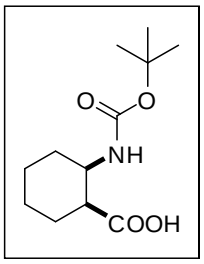
^{13}C NMR: (75 MHz, D_2O) δ 176.52 (C=O) 52.68 (CH) 45.46 (CH) 29.67 (CH_2) 27.19 (CH_2) 21.19 (CH_2) ppm

13.1.5 (±)-*CIS*-N-BOC-2-AMINOCYCLOHEXANECARBOXYLIC ACID **II.175-A**



II.174-a **II.175-a**

The β-amino acid salt **II.174-a** (19.9 g, 111 mmol, 1 eq) is dissolved in a mixture of 180 ml of water and 180 ml of dioxane, followed by the addition of K_2CO_3 (15.3 g, 111 mmol, 1 eq). After cooling to 0°C, a solution of Boc_2O (24.1 g, 111 mmol, 1 eq) in 180 ml of dioxane is added dropwise to this reaction mixture and allowed to stir further for 16 h at room temperature. Subsequently, the reaction mixture is acidified to pH 1-2 with a 1 M solution of HCl, poured into a separating funnel with 270 ml of water and extracted 3x with 500 ml of EtOAc. The collected organic phases are then washed with 800 ml of brine, dried over $MgSO_4$ and evaporated under reduced pressure to yield a yellow oil. This crude product is then purified using column chromatography (eluens: pentane/ethyl acetate/HOAc 90/10/1), delivering the Boc protected amino acid **II.175-a** as a yellowish powder in 71% yield.



Formula: $C_{12}H_{21}NO_4$

Molecular weight: 243,30 g/mol

Yield: 71%

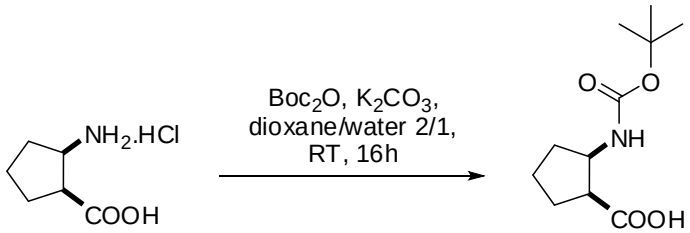
LC-MS:
t_{ret} = 17,6 min
ES-MS [m/z (fragment, intensity)]: 242,1 ($M\text{-}H^+$, 100)

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 5.35 (app. s, 1 H) 3.83 (m, 1 H) 2.83 (m, 1 H) 2.04 (m, 1 H) 1.83-1.55 (m, 4 H) 1.53-1.27 (m, 12 H)

^{13}C NMR: (75 MHz, CHLOROFORM-*d*) δ 179.71 (C=O) 155.52 (C=O) 79.64 (C) 49.36 (CH) 44.97 (CH) 29.94 (CH_2) 28.55 (CH_3) 27.47 (CH_2) 24.37 (CH_2) 22.56(CH_2) ppm

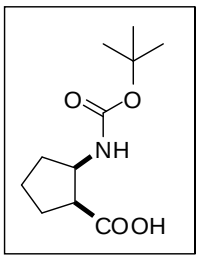
TLC: R_f = 0,25 (pentane/EtOAc/AcOH 80/20/1)

13.1.6 (±)-*CIS*-N-BOC-2-AMINOCYCLOPENTANECARBOXYLIC ACID **II.175-B**



II.174-b **II.175-b**

The β-amino acid salt **II.174-b** (16.2 g, 98.0 mmol, 1 eq) is dissolved in a mixture of 160 ml of water and 160 ml of dioxane, followed by the addition of K_2CO_3 (13.5 g, 98.0 mmol, 1 eq). After cooling to 0°C, a solution of Boc_2O (21.4 g, 98.0 mmol, 1 eq) in 100 ml of dioxane is added dropwise to this reaction mixture and allowed to stir further for 16 h at room temperature. Subsequently, the reaction mixture is acidified to pH 1-2 with a 1 M solution of HCl, poured into a separating funnel with 180 ml of water and extracted 3x with 400 ml of EtOAc. The collected organic phases are then washed with 500 ml of brine, dried over $MgSO_4$ and evaporated under reduced pressure to yield a yellow oil. This crude product is then purified using column chromatography (eluens: pentane/ethyl acetate/HOAc 90/10/1), delivering the Boc protected amino acid **II.175-b** as a yellow powder in 84% yield.



Formula: $C_{11}H_{19}NO_4$

Molecular weight: 229,27 g/mol

Yield: 84%

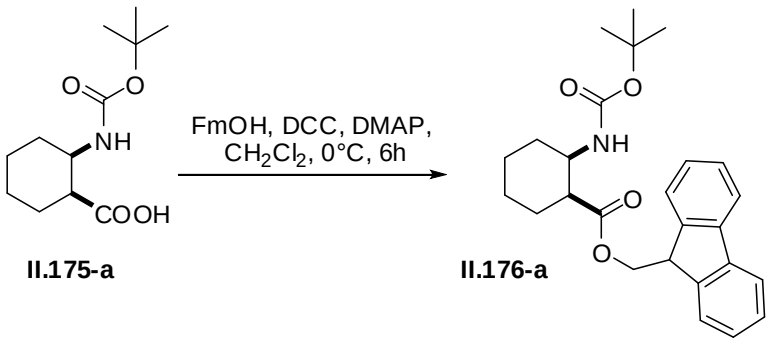
LC-MS:
t_{ret} = 10,3 min
ES-MS [m/z (fragment, intensity)]: 228,1 ($M-H^+$, 100)

^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 6.80 (d, 1 H) 4.16 (m, 1 H) 3.08 (m, 1 H) 2.17-1.78 (m, 4 H) 1.78-1.60 (m, 1 H) 1.59-1.34 (m, 10 H)

^{13}C NMR: (75 MHz, CHLOROFORM-*d*) δ 174.94 (C=O) 155.41 (C=O) 54.13 (CH) 46.93 (CH) 32.01 (CH_2) 28.04 (CH_3) 27.50 (CH_2) 22.11 (CH_2) ppm

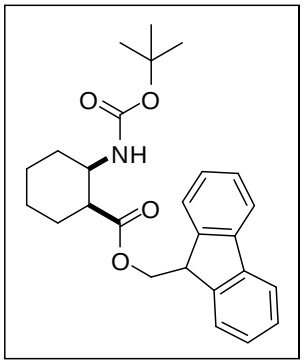
TLC: R_f = 0,12 (pentane/EtOAc/AcOH 80/20/1)

13.1.7 FLUORENYLMETHYLESTER OF (±)-*CIS*-N-BOC-2-AMINOCYCLOHEXANECARBOXYLIC ACID **II.176-A**



II.175-a **II.176-a**

II.175-a (18.9 g, 77.8 mmol, 1 eq) is soluted in 590 ml of CH_2Cl_2, followed by the addition of fluorenylmethanol (13.2 g, 77.8 mmol, 1 eq). After cooling this reaction mixture to 0°C, DMAP (1.9 g, 15.6 mmol, 0.2 eq) and DCC (16.1 g, 77.8 mmol, 1 eq) are added. This solution is allowed to stir for 6 h at 0°C under Ar atmosphere. The formed white precipitate is then filtered off, the filtrate washed with 400 ml of a 1 M HCl solution and 400 ml of brine, dried over $MgSO_4$ and evaporated under reduced pressure. The product is purified using column chromatography (eluens: hexane/ethylacetate 95/5), yielding the product **II.176-a** as a yellow oil in 87% yield.



Formula: $C_{26}H_{31}NO_4$

Molecular weight: 421,53 g/mol

Yield: 87%

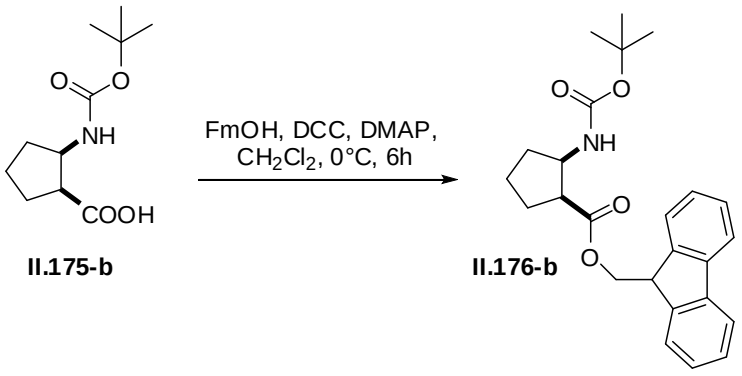
LC-MS:
t_{ret} = 12,9 min (Method B)
ES-MS [m/z (fragment, intensity)]: 242,1 ($M-H^+$-Fm, 100)

^{1}H NMR (300 MHz, CHLOROFORM-*d*) d ppm 7.78 (d, *J*=7.3 Hz, 2 H) 7.60 (t, *J*=7.3 Hz, 2 H) 7.38 - 7.46 (m, 2 H) 7.30 - 7.37 (m, 2 H) 5.20 (d, *J*=9.2 Hz, 1 H) 4.47 - 4.52 (m, 2 H) 4.23 (t, *J*=6.4 Hz, 1 H) 3.80 (br. s., 1 H) 2.85 (q, *J*=4.5 Hz, 1 H) 1.97 (d, *J*=13.6 Hz, 1 H) 1.51 - 1.68 (m, 4 H) 1.39 - 1.46 (m, 9 H) 1.28 - 1.39 (m, 2 H) 1.00 - 1.19 (m, 1 H)

^{13}C NMR: (75 MHz, CHLOROFORM-*d*) δ 173.91 (C=O) 155.25 (C=O) 143.90 (C) 141.39 (C) 127.78 (CH) 127.14 (CH) 124.81 (CH) 120.05 (CH) 79.12 (C) 66.03 (CH_2) 49.18 (CH) 46.95 (CH) 44.93 (CH) 29.50 (CH_2) 28.42 (CH_3) 27.36 (CH_2) 24.14 (CH_2) 22.24(CH_2) ppm

TLC: R_f = 0,57 (isooctane/EtOAc 50/50)

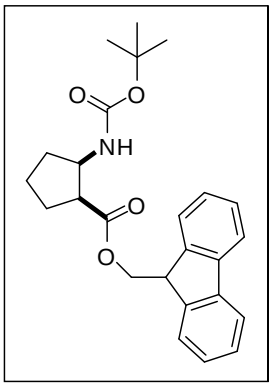
13.1.8 FLUORENYLMETHYLESTER OF (±)-*CIS*-N-BOC-2-AMINOCYCLOPENTANECARBOXYLIC ACID **II.176-B**



II.175-b **II.176-b**

II.175-b (18.8 g, 82.1 mmol, 1 eq) is soluted in 620 ml of CH_2Cl_2, followed by the addition of fluorenylmethanol (13.9 g, 82.1 mmol, 1 eq). After cooling this reaction mixture to 0°C, DMAP (2.0 g, 16.4 mmol, 0.2 eq) and DIC (12.7 ml, 82.1 mmol, 1 eq) are added. This solution is allowed to stir for 6 h at 0°C under Ar atmosphere. The formed white precipitate is then filtered off and the filtrate evaporated under reduced pressure, delivering a greenish oil. This crude product is purified using

column chromatography (eluens: hexane/acetone 95/5), yielding the product **II.176-b** as a yellow oil in 79% yield.



Formula: $C_{25}H_{29}NO_4$

Molecular weight: 407,50 g/mol

Yield: 79%

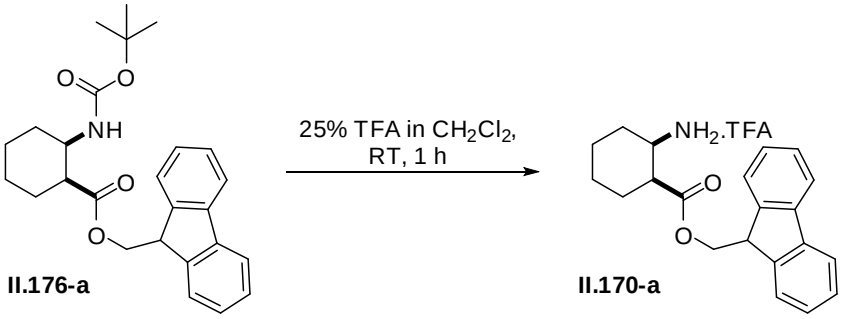
LC-MS:
t_{ret} = 11,0 min (method B)
ES-MS [m/z (fragment, intensity)]: 308,1 ($M+H^+$-Boc, 90), 179,1 (dibenzofulvene+H^+, 5), 130.1 ($M+H^+$-Boc-Fm, 5)

^{1}H NMR (300 MHz, CHLOROFORM-*d*) d ppm 7.78 (d, *J*=7.5 Hz, 2 H) 7.61 (dd, *J*=10.5, 7.6 Hz, 2 H) 7.42 (t, *J*=7.0 Hz, 2 H) 7.33 (tt, *J*=7.3, 1.5 Hz, 2 H) 4.86 (br. s., 1 H) 4.40 - 4.52 (m, 2 H) 4.23 (t, *J*=6.6 Hz, 2 H) 3.06 (q, *J*=7.2 Hz, 1 H) 1.78 - 2.04 (m, 3 H) 1.47 - 1.76 (m, 3 H) 1.41 (s, 9 H)

^{13}C NMR: (75 MHz, CHLOROFORM-*d*) δ 174.25 (C=O) 155.30 (C=O) 144.00 (C) 143.54 (C) 141.38 (CH) 141.24 (CH) 127.80 (CH) 127.74 (CH) 127.19 (CH) 127.13 (CH) 125.04 (CH) 124.83 (CH) 120.01 (CH) 119.97 (CH) 79.24 (C) 66.19 (CH_2) 53.72 (CH) 46.85 (CH) 31.91 (CH_2) 28.37 (CH_3) 27.94 (CH_2) 21.99 (CH_2) ppm

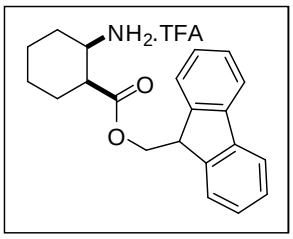
TLC: R_f = 0,12 (hexane/acetone 95/5)

13.1.9 FLUORENYLMETHYLESTER OF (±)-*CIS*-2-AMINOCYCLOHEXANECARBOXYLIC ACID **II.170-A**



II.176-a **II.170-a**

The double protected β-amino acid **II.175-a** (28.5 g, 67.6 mmol, 1 eq) is soluted in 450 ml of CH_2Cl_2, followed by the addition of 150 ml of TFA. This reaction mixture is subsequently allowed to stir for 1 h at room temperature, before it is evaporated under reduced pressure. The residual TFA is azeotropically removed by evaporation under reduced pressure in the presence of CH_3CN. Adding diethylether to this crude mixture allows to precipitate the pure product **II.170-a** as a white powder in 92% yield.



Formula: $C_{23}H_{24}F_3NO_4$

Molecular weight: 435,44 g/mol

Yield: 92%

LC-MS:

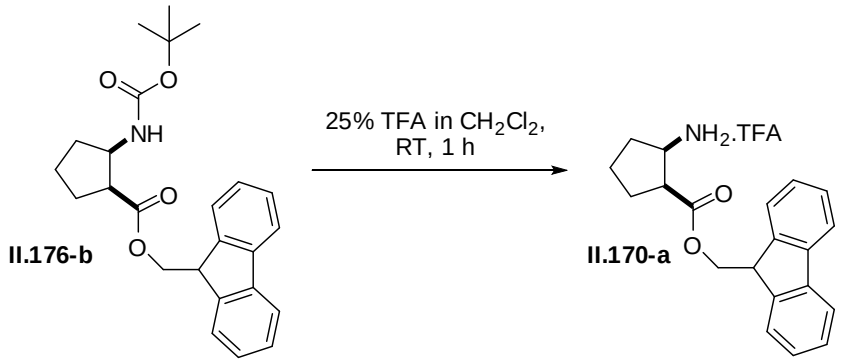
t_{ret} = 15,7 min

ES-MS [m/z (fragment, intensity)]: 322,1 ($M+H^+$, 94), 179,1 (dibenzofulvene+H^+, 2), 144.1 ($M+H^+$-Boc-Fm, 4)

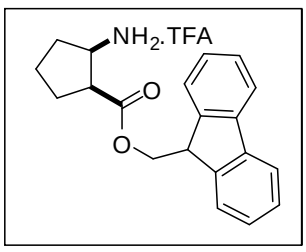
^{1}H NMR (300 MHz, METHANOL-*d*$_4$) δ ppm 7.74 - 7.87 (m, 2 H) 7.55 - 7.69 (m, 2 H) 7.25 - 7.47 (m, 4 H) 4.77 - 4.87 (m, 1 H) 4.51 - 4.66 (m, 1 H) 4.28 (d, *J*=4.3 Hz, 1 H) 3.28 (d, *J*=4.5 Hz, 1 H) 2.86 (d, *J*=4.5 Hz, 1 H) 1.13 - 1.86 (m, 7 H) 0.89 (m, 1 H)

^{13}C NMR: (75 MHz, CHLOROFORM-*d*) δ 174.45 (C=O) 145.20 (C) 145.03 (C) 142.94 (C) 142.82 (C) 129.24 (CH) 128.40 (CH) 128.32 (CH) 126.09 (CH) 126.00 (CH) 121.20 (CH) 121.12 (CH) 67.55 (CH_2) 51.21 (CH) 48.38 (CH) 47.64 (CH_2) 30.94 (CH_3) 29.66 (CH_2) 25.45 (CH_2) 24.82 (CH_2) ppm

13.1.10 FLUORENYLMETHYLESTER OF (±)-CIS-2-AMINOCYCLOPENTANECARBOXYLIC ACID **II.170-B**



The double protected β-amino acid **II.175-b** (26.3 g, 67.6 mmol, 1 eq) is soluted in 230 ml of CH_2Cl_2, followed by the addition of 77 ml of TFA. This reaction mixture is subsequently allowed to stir for 1 h at room temperature, before it is evaporated under reduced pressure. The residual TFA is azeotropically removed by evaporation under reduced pressure in the presence of CH_3CN. Adding diethylether to this crude mixture allows to precipitate the pure product **II.170-b** as a white powder in 89% yield.



Formula: $C_{22}H_{22}F_3NO_4$

Molecular weight: 421,41 g/mol

Yield: 89%

LC-MS:

t_{ret} = 15,4 min

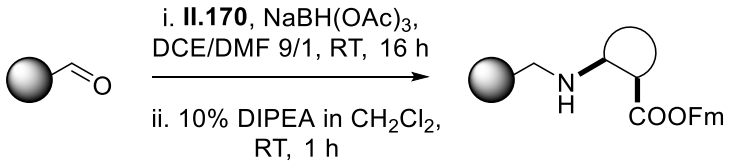
ES-MS [m/z (fragment, intensity)]: 308,1 ($M+H^+$, 90), 179,1 (dibenzofulvene+H^+, 5), 130.1 ($M+H^+$-Fm, 5)

^{1}H NMR (300 MHz, METHANOL-d_4) d ppm 7.82 (d, *J*=7.3 Hz, 2 H) 7.65 (t, *J*=6.6 Hz, 2 H) 7.38 - 7.49 (m, 2 H) 7.26 - 7.38 (m, 2 H) 4.73 (dd, *J*=6.3, 4.4 Hz, 1 H) 4.51 (dd, *J*=10.7, 5.7 Hz, 1 H) 4.21 - 4.34 (m, 1 H) 3.62 - 3.74 (m, 1 H) 2.94 - 3.11 (m, 1 H) 1.85 - 2.25 (m, 2 H) 1.57 - 1.83 (m, 4 H)

^{13}C NMR: (75 MHz, CHLOROFORM-*d*) δ 174.33 (C=O) 145.31 (C) 145.02 (C) 142.94 (C) 142.82 (C) 129.12 (CH) 129.09 (CH) 128.41 (CH) 128.36 (CH) 126.14 (CH) 126.04 (CH) 121.18 (CH) 67.53 (CH_2) 54.05 (CH) 48.28 (CH) 46.70 (CH) 31.07 (CH_2) 28.84 (CH_2) 22.61 (CH_2) ppm

13.2 SYNTHESIS OF 3,4-DIHYDRO-2*H*-1,2,6-THIADIAZOCIN-5(6*H*)-ONE-1,1-DIOXIDES

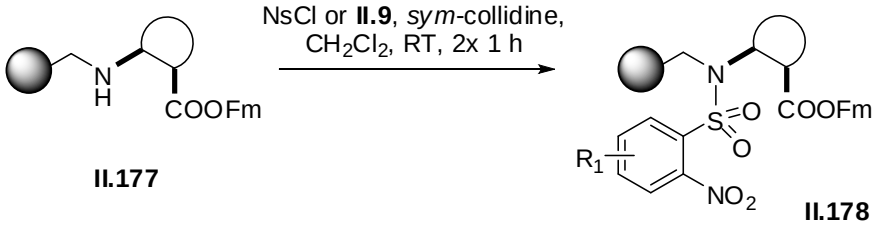
13.2.1 COUPLING OF THE β-AMINO ACID



II.70 **II.177**

The FMPB resin **II.70** (1.00 g, 0.79 mmol, 1 eq) is preswollen 2x 20 min in 10 ml of CH_2Cl_2. Subsequently, 16 ml of 1,2-dichloroethane, 2 ml of DMF, β-amino acid **II.170-(a-b)** (0.997 g, 2.37 mmol, 3 eq) and $NaBH(OAc)_3$ (0.251 g, 1.18 mmol, 4.5 eq) are added to the FMPB-resin and this suspension is shaken for 16 h. The resin is then washed 3x with DMF, MeOH and CH_2Cl_2. To remove the TFA from the resin after coupling, the resin was shaken 2x 1 h in the presence of a 10% DIPEA solution in CH_2Cl_2 and washed 3x again with DMF, MeOH and CH_2Cl_2.

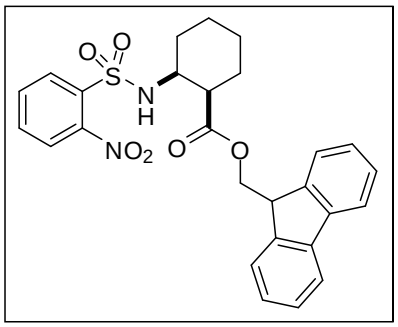
13.3 COUPLING OF *ORTHO*-NOSYL CHLORIDE



II.177 **II.178**

To the solid supported β-amino acid **II.177** (0.575 g, 0.42 mol, 1 eq), suspended in 10 ml CH_2Cl_2, is consecutively added *sym*-collidine (0.276 ml, 2.09 mmol, 5 eq) and *o*-nosyl chloride or **II.9** (1.05 mmol, 2.5 eq). This suspension is shaken for 1 h at room temperature and thereafter washed 3x with DMF, MeOH and CH_2Cl_2. Then this coupling procedure is repeated for a second time, yielding the solid supported nosyl protected β-amino acid **II.178**.

This reaction was optimized for compound **II.177**, with ACHC as β-amino acid and R_1 = H. LC-MS analysis after cleavage delivered the following result:

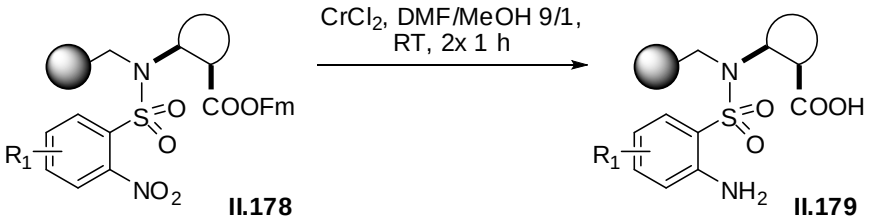


Formula: $C_{27}H_{26}N_2O_6S$

Molecular weight: 506,57 g/mol

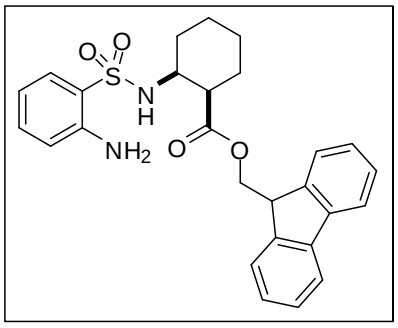
LC-MS:
t_{ret} = 9,9 min (Method B)
ES-MS [m/z (fragment, intensity)]: 327,0 ($M\text{-}H^+$-Fm, 100)

13.4 NITRO REDUCTION



To a suspension of compound **II.178** in 6 ml of a 9/1 mixture of DMF/MeOH, is added chromium(II) chloride (0.411 g, 3.34 mmol, 8 eq) in one portion. This reaction mixture is allowed to shake for 1 h, followed by filtration and washing the resin 3x with DMF, MeOH and CH_2Cl_2. This procedure is repeated for a second time, delivering the desired aniline **II.179**.

This reaction was optimized for compound **II.178**, with ACHC as β-amino acid and R_1 = H. LC-MS analysis after cleavage delivered the following result:



Formula: $C_{27}H_{28}N_2O_4S$

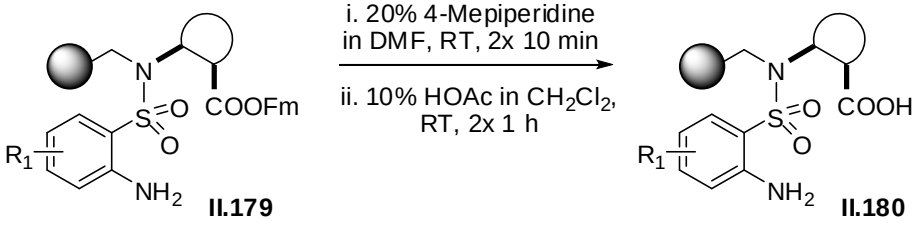
Molecular weight: 476,59 g/mol

LC-MS:

t_{ret} = 19,7 min

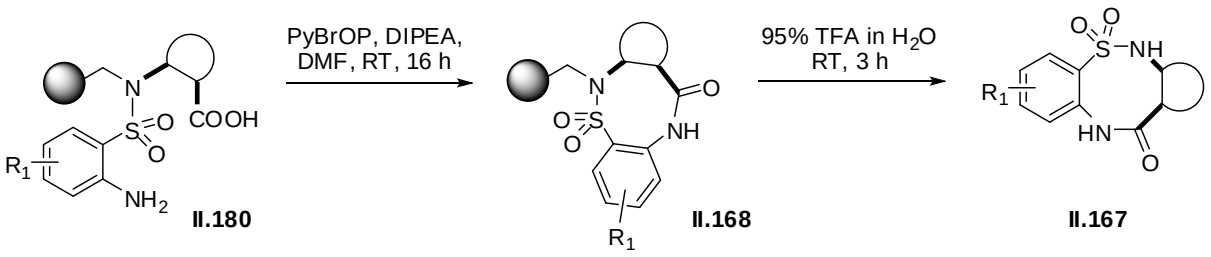
ES-MS [m/z (fragment, intensity)]: 477,1 ($M+H^+$, 100)

13.5 FM REMOVAL



Compound **II.179** is suspended in a 20% solution of 4-methylpiperidine in DMF, shaken for 10 min at room temperature and subsequently filtered off and washed 3 times with DMF, MeOH and CH_2Cl_2. This procedure is repeated for a second time, followed by the removal of residual 4-methylpiperidine by shaking the resin 2x in the presence of a 10% acetic acid solution in CH_2Cl_2. This readily delivered ring closing precursor **III.180**.

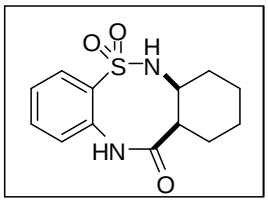
13.6 ON-RESIN CYCLIZATION AND CLEAVAGE



II.180 **II.168** **II.167**

The resin **II.180** (0.42 mmol, 1 eq) is suspended in 12 ml DMF, followed by the consecutive addition of DIPEA (0.728 ml, 4.2 mmol, 10 eq) and PyBrOP (974 mg, 2.09 mmol, 5 eq). This suspension is shaken for 16 h at room temperature, then filtrated and washed 3x with DMF, MeOH and CH_2Cl_2. The ring closed product **II.168** is subsequently cleaved from the solid support by shaking the resin for 3 h in a 95% solution of TFA in water at room temperature. The resin was then filtered off, the filtrate collected in a flask and evaporated under reduced pressure, readily delivering the benzothiadiazocinon **II.167**. These crude products were purified with column chromatography.

13.6.1 3,4-DIHYDRO-2*H*-[C]CYCLOHEXANYL-1,2,6-BENZOTHIADIAZOCIN-5(6*H*)-ONE-1,1-DIOXIDE **II.167-A**



Formula: $C_{13}H_{16}N_2O_3S$

Molecular weight: 280,34 g/mol

Yield: 7%

LC-MS:

t_{ret} = 13,4 min (method A)

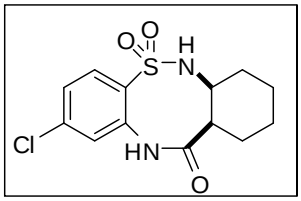
ES-MS [m/z (fragment, intensity)]: 279,1 ($M\text{-}H^+$, 100)

^{1}H NMR: (300 MHz, DMSO-d_6) δ ppm 9.77 (s, 1 H) 8.36 (d, *J*=8.3 Hz, 1 H) 7.83 (d, *J*=7.9 Hz, 1 H) 7.54 (t, *J*=7.3 Hz, 1 H) 7.39 (t, *J*=7.5 Hz, 1 H) 7.18 (d, *J*=7.7 Hz, 1 H) 3.69 (br. s., 2 H) 2.86 - 3.09 (m, 1 H) 1.95 - 2.20 (m, 1 H) 1.49 - 1.84 (m, 4 H) 1.18 - 1.42 (m, 3 H)

^{13}C NMR: (75 MHz, CHLOROFORM-*d*) δ 174.33 (C=O) 145.31 (C) 145.02 (C) 142.94 (C) 142.82 (C) 129.12 (CH) 129.09 (CH) 128.41 (CH) 128.36 (CH) 126.14 (CH) 126.04 (CH) 121.18 (CH) 67.53 (CH_2) 54.05 (CH) 48.28 (CH) 46.70 (CH) 31.07 (CH_2) 28.84 (CH_2) 22.61 (CH_2) ppm

TLC: 0,04 (hexane/ethyl acetate 70/30)

13.6.2 8-CHLORO-3,4-DIHYDRO-2*H*-[C]CYCLOHEXANYL-1,2,6-BENZOTHIADIAZOCIN-5(6*H*)-ONE-1,1-DIOXIDE **II.167-B**



Formula: $C_{13}H_{15}ClN_2O_3S$

Molecular weight: 314,79 g/mol

Yield: 4%

LC-MS:

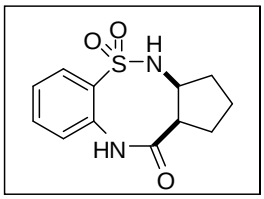
t_{ret} = 14,8 min (method A)

ES-MS [m/z (fragment, intensity)]: 313,0 ($M\text{-}H^+$, 100)

^{1}H NMR: (300 MHz, DMSO-d_6) δ ppm 9.83 (br. s., 1 H) 8.50 (d, *J*=7.9 Hz, 1 H) 7.84 (d, *J*=8.7 Hz, 1 H) 7.47 (d, *J*=8.5 Hz, 1 H) 7.24 (s, 1 H) 3.50 (br. s., 2 H) 3.02 (br. s., 1 H) 1.99 - 2.17 (m, 1 H) 1.51 - 1.85 (m, 3 H) 1.20 - 1.42 (m, 3 H)

^{13}C NMR: (75 MHz, CHLOROFORM-*d*) δ 173.11 (C=O) 136.31 (C) 134.63 (C) 130.18 (CH) 126.51 (CH) 126.45 (CH) 52.17 (CH) 37.22 (CH) 27.23 (CH_2) 25.34 (CH_2) 24.49 (CH_2) 20.64 (CH_2) ppm
Quaternairy aromatic carbon on position 8 not visible (not enough product)

13.6.3 3,4-DIHYDRO-2*H*-[C]CYCLOPENTANYL-1,2,6-BENZOTHIADIAZOCIN-5(6*H*)-ONE-1,1-DIOXIDE **II.167-C**



Formula: $C_{13}H_{16}N_2O_3S$

Molecular weight: 266,32 g/mol

Yield: 7%

LC-MS:

t_{ret} = 4,6 min (method C)

ES-MS [m/z (fragment, intensity)]: 265,1 ($M\text{-}H^+$, 100)

^{1}H NMR: (300 MHz, METHANOL-d_4) δ ppm 7.99 (dd, *J*=8.0, 1.4 Hz, 1 H) 7.77 (s, 1 H) 7.56 (td, *J*=7.7, 1.7 Hz, 1 H) 7.43 (td, *J*=7.9, 1.3 Hz, 1 H) 7.18 (dd, *J*=7.7, 0.9 Hz, 1 H) 3.62 - 3.78 (m, 1 H) 2.81 - 2.95 (m, 1 H) 2.17 (dtd, *J*=12.9, 8.5, 8.5, 4.3 Hz, 1 H) 1.87 - 2.00 (m, 1 H) 1.66 - 1.81 (m, 1 H) 1.34 - 1.60 (m, 3 H)

^{13}C NMR: (75 MHz, CHLOROFORM-*d*) δ 175.11 (C=O) 137.78 (C) 134.59 (CH) 133.91 (C) 131.57 (CH) 129.23 (CH) 128.94 (CH) 56.63 (CH) 43.12 (CH) 32.81 (CH_2) 25.79 (CH_2) 23.31 (CH_2) ppm

TLC: 0,12 (hexane/ethyl acetate 50/50)